Original Research Article

Study of prevalence of insulin resistance in non-diabetes hypertensive patients attending medicine OPD at a tertiary care center

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Abstract

Background: The patients with essential hypertension are increasing all over the world. There may be development of insulin resistance and hyperinsulinemia in essential hypertension. An association between essential hypertension and defective insulin secretion has been identified. Insulin resistance is the fundamental defect in the development of type 2 diabetes mellitus, hypertension and cardiovascular diseases. **Objectives:** To study the prevalence of insulin resistance in non-diabetes hypertensive patients **Material and Methods:** A total of 100 patients were taken, 50 each were divided into cases and controls. Appropriate investigations were done. Insulin resistance was determined by HOMA-IR (homeostasis model assessment of insulin resistance). **Results:** Statistically, the mean value of HOMA-IR in cases was 3.9 ± 1.92 and in healthy group was 2.1 ± 0.7 with $p<0.05$. Also study found waist circumference, BMI, FBS, TG, fasting plasma insulin showed significant association in hypertension group subjects **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 significance with BMI, insulin resistance being the likely predominant mechanism.

Key Words: Insulin resistance, essential hypertension, metabolic syndrome.

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Received Date: 21/08/2018 Revised Date: 12/09/2018 Accepted Date: 02/10/2018
DOI: https://doi.org/10.26611/1021815

Access this article online

Quick Response Code:

Website: www.medpulse.in

Accessed Date: 02 October 2018

INTRODUCTION

Insulin is an anabolic hormone that plays an important role in the regulation of glucose, lipid homeostasis and energy storage through its metabolic effects on classic insulin-responsive tissues.[1] Specifically, insulin promotes the storage of glucose as glycogen in liver and skeletal muscles, and facilitates deposition of fatty acids in the form of triglycerides in adipose tissue.[2] During insulin resistance, insulin-mediated anabolic metabolic effects are inhibited in the classic insulin-responsive tissues. Hypertension is a recognized modifiable risk factor of cardiovascular disease (CVD), stroke and end stage renal disease. The prevalence of hypertension has increased in young men than in women.[3] Patients with arterial hypertension and no definable cause are said to have primary, essential or idiopathic hypertension.[4] As per new guideline for the prevention, detection, evaluation, and management of high blood pressure in adults published by American college of cardiology 2017 a hypertension stage 1 means a systolic blood pressure of 130–139 mm hg or 80–89 mm Hg diastolic blood pressure and stage 2 refers to systolic blood pressure of ≥140 mm hg or diastolic of ≥90 mm Hg.[3] 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.[1] Epidemiological studies have shown that hypertension is present in 25% of urban and 10% of rural patients in India.[6] Hypertension is an important CVD risk factor with high global prevalence.[7] It is one of the most commonly identified components of the MetS.[8,9] Metabolic syndrome (MetS) is a cluster of

How to cite this article: K V Giriraja, Madhusudan C. Study of prevalence of insulin resistance in non-diabetes hypertensive patients attending medicine OPD at a tertiary care center. *MedPulse International Journal of Medicine.* October 2018; 8(1): 25-29. https://www.medpulse.in/Medicine/

multiple metabolic abnormalities that increases the risk of cardiovascular morbidity and mortality.[13,14] The cluster includes various combinations of elevated blood pressure (BP), atherogenic dyslipidemia, obesity, abnormal glucose tolerance and insulin resistance (IR).[14] When hypertension and other metabolic risk factors co-exist in an individual, they potentiate one another leading to a synergism that increases the total CVD risk well above that which results from the sum of the individual risk factors. Recognition of this fact has led to a reorientation with regard to risk stratification and management of hypertension.[10] 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 Na+ H+ exchange and resultant intracellular accumulation of Na+ and 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.[11,12] 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.[18] 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.[15-18]

MATERIAL AND METHODS

In this cross sectional study, a total of 100 patients was enrolled out of which 50 hypertensive subjects as per the latest American college of cardiology adult hypertension guidelines 2017 and 50 healthy subjects aged more than 18 years attending the OPD of Department of Internal Medicine, Sapthagiri Institute of Medical Sciences and Research Center, Bengaluru for routine health check-up were enrolled. According to latest American college of cardiology adult hypertension guidelines 2017hypertension was defined[5]. Healthy subjects without hypertension, impaired fasting glucose, impaired glucose tolerance, diabetes mellitus served as control. After fulfilling the inclusion and exclusion criteria, the patient were enrolled in this study. 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.

Table 1: Annexure A: The new International Diabetes Federation (IDF) definition[19]

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have: Central obesity (defined as waist circumference* with ethnicity specificvalues) plus any two of the following four factors:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific c treatment for this lipid abnormality
educed HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

The DRG insulin enzyme immunoassay kit provides materials for the quantitative determination of insulin. Insulin resistance can be estimated using several techniques. The euglycaemic hyperinsulinemic clamp technique is the gold standard method for evaluation.[20] But HOMA-IR is a simple and reliable surrogate measure of insulin resistance.[19,20]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.[21] Fasting insulin (uIU/ml) × fasting glucose (mmol/l)/22.5 or fasting insulin (uIU/ml) × fasting glucose (mg/dl)/405. After calculating insulin resistance, insulin resistance was categorized into normal, moderate and severe insulin resistance as follows.

Table 2: Annexure B

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

RESULTS

Table 3: Age, anthropometric and metabolic profile of study subjects

Parameter	Hypertensive subjects (n = 50)	Control (n = 50)	p-value
Age (years)	53.83±10.4	52.10±9.3	>0.05
Waist circumference (cm)	88.62±8.7	81.59±4.7	<0.05
BMI (kg/m^2)	24.36±1.2	22.92±1.0	<0.05
FBS (mg/dl)	92.17±3.6	88.77±2.8	<0.05
HbA1c (%)	5.05±0.2	5.05±0.2	>0.05
Triglycerides (mg/dl)	192.81±32.4	122.25±28.2	<0.05
High density lipoprotein (mg/dl)	46.11±6.6	41.75±8.0	>0.05
Low density lipoprotein (mg/dl)	107.60±15.0	103.89±15.2	>0.05
Cholesterol (mg/dl)	135.32±21.2	132.00±17.4	>0.05
Fasting plasma insulin (µIU/ml)	16.08±9.1	8.32±3.6	<0.05
Insulin resistance (HOMA-IR)	3.9 ± 1.9	2.1 ± 0.7	<0.05

In our study age factor did not show any significance, while waist circumference, BMI, FBS, TG, fasting plasma insulin, and insulin resistance showed significant association in hypertension group subjects when compared to healthy group subjects.(p <0.05 significant), also HBA1c%, HDL, LDL, Cholesterol did not show any significant association in two groups.

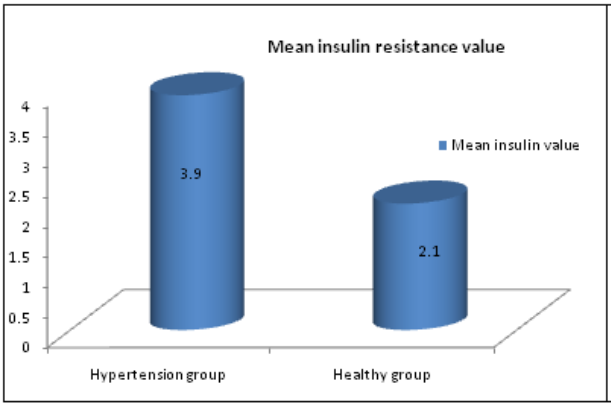

Figure 1

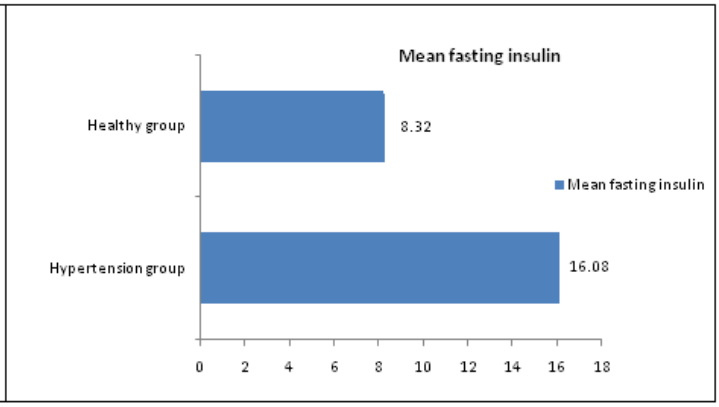

Figure 2

Figure 1: Bar diagram showing comparison of mean insulin resistance between study groups; **Figure 2:** Bar diagram showing comparison of mean fasting plasma insulin between hypertensive and control group. In this study fasting plasma insulin levels were significantly higher in hypertension group than healthy group.

The mean insulin resistance value in hypertension group (3.9) was significantly higher when compared to healthy group (2.1).

DISCUSSION

The study was conducted in Department of Internal Medicine, Sapthagiri Institute of Medical Sciences and Research Center, Bengaluru 50 hypertensive patients were compared with 50 non-hypertensive healthy subjects. Out of 50 patients in each group, 52% (n = 26) were male and 48% (n = 24) were females, mean age of patients in hypertensive group was 53.83±10.4 years, while in healthy group was 52.10±9.3 years. Among the 50 hypertensive patients, 48% (n = 24) patients belonged to rural background while in healthy group 52% (n = 26) subjects were from rural background which shows equal distribution of cases and controls in the study. Family history of hypertension in first degree relatives was more common in hypertensive group. The mean BMI in hypertensive urban patients was 24.36±1.2 kg/m2 while in rural hypertensive patients mean BMI was 22.92±1.0 kg/m2 which was statistically significant (p <0.05). Insulin resistance and compensatory hyperinsulinemia commonly occur in patients with untreated essential hypertension. The coexistence of insulin resistance and

hypertension can be viewed as a cause-effect relationship (insulin resistance as a cause of hypertension or vice versa) or as a noncausal association. Insulin can increase blood pressure via several mechanisms: increased renal sodium reabsorption, activation of the sympathetic nervous system, alteration of transmembrane ion transport, and hypertrophy of resistance vessels. Conversely, hypertension can cause insulin resistance by altering the delivery of insulin and glucose to skeletal muscle cells, resulting in impaired glucose uptake.[24]As insulin resistance develop long before systemic diseases appear; identification and treating insulin resistance have great preventive value. Gupta AK *et al*[25] said that measuring insulin level alone in a single fasting sample can serve as a simple, cheap, and convenient indirect qualitative index of insulin resistance. We also did the same in this study. Sinha S *et al*[26] study the mean (± SD) FSI level in hypertensive patients was higher than that of controls, which was statistically highly significant ($p<0.001$), similar was seen in our study with mean plasma insulin in hypertensive group was 8.32±3.6 which was statistically significant as compared to healthy controls. Insulin resistance in Indian population ranges from 5-50%. The tremendous heterogenecity in Indian in terms of insulin resistance is related to our different lifestyles, dietary habits and different socio-economic status.[27] In this study, in controls group only 14% (n = 7) had moderate insulin resistance the while in hypertensive group64% (n = 32) cases had moderate to severe insulin resistance. Insulin resistance in hypertension had been reported and overall prevalence was around 50%. Similar results were seen in study done by Chug *et al*[26] who demonstrated relationship of insulin resistance and hypertension in north Indian non diabetic subjects. Similar findings were also seen Mohan *et al*[29] study. End-organ damage, particularly hypertensive retinopathy and left ventricular hypertrophy, had been observed in patients with hypertension. While Nereida KC *et al*[30] in their study said said 50% of patients could be considered to be sufficiently insulin resistant to be at increased risk of adverse clinical outcomes, irrespective of treatment status. Also SinhaS *et al*[26] study concluded that HOMA-IR was significantly higher in hypertensive group than that of the control group, which was in accordance with our study. In recent years, insulin resistance has gain importance as its role in the pathogenesis of many metabolic disorders. The insulin resistance syndrome is a syndrome which includes multiple disorders like hypertension, changes in atherogenic lipoproteins, diabetes, and hypercoagulability. Hypertensive subjects having all the four parameters of metabolic syndrome had higher mean insulin levels (24.9±5.80 μIU/ml) and hence higher insulin resistance (5.62±1.32) as compared to patients having three parameters. In our study 48% (n = 24) of hypertensive patients had metabolic syndrome when compared to control group in whom only 10% (n = 5) had metabolic syndrome, suggesting that metabolic syndrome is more prevalent in hypertensive subjects. A similar results were seen in a study done by Salagre SB *et al*[31]in which they concluded that 49.07% of hypertensive subjects had metabolic syndrome. A study done by Alves LMM *et al*[32] found similar results with 60.7% hypertensive subjects had metabolic syndrome, but a bit higher percentage was seen in Makwana D *et al*[33] study with metabolic syndrome among hypertensive patients of 55.23%.Japanese researchers Kanauchi M *et al*[34] reported a positive correlation between MetS prevalence and BP in a study involving 506 untreated hypertensive patients. Sinha S *et al*[26] study reported mean lipid profile higher in hypertensive group than that of the control group which was statistically not significant, this was similar with our study results. Rural-urban difference of insulin resistance is also well known. Similar was seen in our study, urban population had higher fasting serum insulin levels and a higher BMI as compared to rural population and hence higher insulin resistance was seen in urban population. Simialar results were seen in Mohan G *et al* study.[35]

CONCLUSION

It is proven that, insulin resistance is the central feature or the root cause of the metabolic syndrome as it is strongly related to all other components of the metabolic syndrome as well as to elevated proinflammatory markers, thrombogenic factors, and endothelial dysfunction. All of these factors are thought to underlie increased risk of cardiovascular disease. So it is better to diagnose insulin resistance early and appropriate treatment started to prevent premature cardiovascular complication in hypertensive patients.

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Source of Support: None Declared
Conflict of Interest: None Declared