



STUDY OF SERUM INSULIN LEVEL AND ESTIMATION OF INSULIN RESISTANCE BY HOMA-IR METHOD IN PATIENTS OF BENIGN ESSENTIAL HYPERTENSION

Dr Nupur Srivastava Assistant Professor Dept of Physiology Pt JNM Medical College, Raipur CG

Dr PK Khodiar Associate Professor Dept of Biochemistry Pt JNM Medical College, Raipur, CG

ABSTRACT

Hyperinsulinemia syndrome describes four conditions—insulin resistance, hyperlipidemia, abdominal obesity, and hypertension—that occur more frequently together than chance alone would dictate. Secondary effects from hyperinsulinemia may cause blood pressure elevations; in fact, hyperinsulinemia is strongly correlated with the development of essential hypertension. Hyperinsulinemia is considered to cause blood pressure elevation and is generally accepted as an independent risk factor for atherosclerosis. It has been revealed previously that insulin-mediated glucose uptake was reduced by 40% in subjects with hypertension. Approximately 50% of hypertensive patients are insulin resistant and these subjects are at great risk of cardiovascular disease. Thus, hypertensive patients with insulin resistance represent a particular disease group and require special medical attention in daily practice. Hence this study is aimed to emphasize how common insulin resistance is in patients with essential hypertension and to reemphasize the need to initiate intensive efforts aimed to improve insulin sensitivity and treating all of the CVD risk factors in patients with essential hypertension, not just the blood pressure.

KEYWORDS : Hyperinsulinemia, Insulin Resistance, HOMA IR, hypertension

INTRODUCTION

Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response; classically this refers to impaired sensitivity to insulin mediated glucose disposal. Compensatory hyperinsulinaemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels.

Although it remains controversial whether elevated insulin, per se, causes blood pressure elevations, elevated insulin levels clearly are associated with increased risk for atherosclerosis, coronary artery disease, and renal decline among patients with hyperinsulinemia syndrome. (Spangler JG et al, 1998). The insulin resistance and hyperinsulinemia associated with hypertension is the result of increased renal tubular sodium reabsorption, increased sympathetic nervous system activity, and increased arterial wall smooth muscle reactivity. In insulin resistant states, intracellular calcium and sodium accumulation is thought to be the fundamental underlying abnormality. (Edelson GW et al, 1993)- The common coexistence of a genetic predisposition for hypertension with insulin resistance helps to explain the frequent occurrence of hypertension as well as dyslipidemia, obesity and diabetes Type 2 in a given individual. Chronically, hyperinsulinemia may promote cardiovascular muscle cell proliferation and atherogenesis. Insulin resistance affecting certain transmembrane cation transporters might lead to an elevation of intracellular cytosolic calcium levels thereby inducing inappropriate vasoconstriction. (Weidmann P et al, 1995)

However, insulin per se does not elevate blood pressure, but rather reduces total peripheral vascular resistance in experimental studies. Blood pressure might be elevated by other mechanisms secondary to hyperinsulinemia, however, such as enhanced renal sodium retention, elevated intracellular free calcium, and increased activity of the sympathetic nervous system. Ferrannini et al. revealed previously that insulin-mediated glucose uptake was reduced by 40% in subjects with hypertension.

Although several methods for assessment of insulin resistance are available, in this study we diagnosed insulin resistance if any of the following conditions are met: BMI >28.9 kg/m², homeostasis model assessment of insulin resistance (HOMA-IR) >4.65 , or BMI >27.5 kg/m² and HOMA-IR >3.60 . The fasting serum insulin concentrations corresponding to these HOMA-IR cut points were 20.7 and 16.3 μ U/ml, respectively. This rule had a sensitivity and specificity of 84.9 and 78.7%, respectively. (Stern SE et al, 2005). Lansang et al. demonstrated that there was significant correlation between results of glucose clamps and HOMA-IR in hypertensive

subjects and suggested to use the index as a surrogate estimate for insulin resistance in hypertension. As extensively discussed by Matthews et al, who developed the HOMA, low HOMA-IR values indicate a high insulin sensitivity, whereas high HOMA-IR values indicate a low insulin sensitivity (insulin resistance). In an Indian study Jhamb R et al, 2005 defined insulin resistance as cases having their HOMA IR levels greater than mean ± 2 SD of the healthy controls. The mean HOMA-IR value among healthy individuals was 1.45 ± 1.34 .

MATERIAL AND METHOD

MATERIAL:

In this study benign essential hypertensive patient (stage 1 or stage 2), as per Seventh Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), OR the patients on antihypertensive medications attending the out patient or admitted in the wards of Medicine Department were selected as cases.

Inclusion criteria for individuals suffering from benign essential hypertension

- Age >18 years.
- Individuals having stage 1 or stage 2 hypertension as per Seventh Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) OR the patients on antihypertensive medications will be included.

Exclusion criteria for individuals suffering from benign essential hypertension

- Age <18 years
- Individuals having type 1 Diabetes
- Individuals having type 2 Diabetes
- Individuals having Secondary hypertension will be excluded as per proforma.
- A. Inclusion criteria for control group
- Individuals in a state of complete physical, mental and social wellbeing and not merely have an absence of disease or infirmity.
- Special care will be taken to exclude any hypertensive patient.

METHOD:

A total of 60 individuals suffering from benign essential hypertension were selected as the study group while a total of 20 healthy individuals were selected for the control group. All subjects underwent complete general and systemic examination. All patients underwent blood pressure examination in sitting position

on 2 or more occasions and average was taken to define them as hypertensive individual. All subjects were investigated for renal function tests (serum urea and creatinine levels), fasting blood glucose, serum insulin and serum lipid profile after overnight fast of 8-12 hours. Both the group were evaluated for fasting insulin levels by an Enzyme linked immunosorbent assay (ELISA) method at the time of entry into the study. The kit had a high specificity (with a cross reactivity with potentially interfering hormones < 10%) and sensitivity of 0.75 μ U/ml at 95% confidence limit. The insulin resistance was calculated by HOMA-IR formula.

Fasting insulin (μ U/ml) x fasting glucose (mmol/l) / 22.5
 Insulin levels were defined as elevated among women if they exceeded 115 pmol/L (16 μ U/mL) and among men if they exceeded 90 pmol/L (12.5 μ U/mL). Statistical association between findings of the study in two groups (study group A and B) was assessed and interpreted.

OBSERVATION

The mean serum insulin level among the study group (14.90 \pm 13.27 μ U/mL) was more than the control group (7.31 \pm 4.20 μ U/mL), which was statistically significant (p = 0.0143). The mean fasting blood sugar level among the study group (95.70 \pm 12.29 mg/dl) was significantly more than the control group (82.55 \pm 8.46 mg/dl). Hyperinsulinemia was present in 26 (43.33%) patients of study group while none of the control cases were hyperinsulinemic which is statistically highly significant (p<0.0001). The prevalence of hyperinsulinemia was found to be increasing with age of the patient.

The mean HOMA-IR level among the study group (3.52 \pm 3.19 mmol/l. μ U/mL) was significantly more than the control group (1.62 \pm 1.10 mmol/l. μ U/mL) Insulin resistance was present in 29 (48.33%) patients of study group while none of the control cases were found to be having insulin resistance. The prevalence of Insulin resistance was found to be increasing with age of the patient. The prevalence of Insulin resistance & hyperinsulinemia was more in stage II hypertensive patients as compared to stage I hypertensive patients.

The lipid profile was found to be more deranged in study group as compared to control group. The mean serum triglyceride in study group (153.21 \pm 55.68 mg/dl) was significantly more than control group (117.55 \pm 28.49 mg/dl). The mean values of other lipids (total cholesterol, HDL & LDL) were also more deranged in study group as compared to control group but were not significant. The number of patients with cholesterol >200 mg/dl, triglyceride >150 mg/dl and abnormal HDL were significantly more in study group (46.66%, 45% & 41.66% respectively) as compared to control group (10% each).

The mean BMI in the study group was significantly more in study group than the control group. In study group out of 60 patients 29 patients had normal BMI. 23(38.33%) patients had BMI of 25-30 as compared to 2(10%) in control group. In study group 7 (11.67%) patients had BMI 30-34.9 and 1 (1.67%) patient had BMI 35-39.9 while none of the patient in control group was having such BMI values.

The mean systolic/diastolic BP was also more in insulin resistant patients than non insulin resistant patients but on analysis found to be insignificant. The mean fasting serum insulin level & fasting blood glucose were significantly more in insulin resistant patients as compared to non insulin resistant patients. The mean serum triglyceride in insulin resistant patients (185.96 \pm 54.62 mg/dl) was significantly more than in non insulin resistant patients (122.58 \pm 36.15 mg/dl) as well as number of patients with triglyceride >150mg/dl were more in insulin resistant than in non insulin resistant patients and this was statistically highly significant (p<0.01). The mean values of other lipids (HDL & LDL) were also more deranged in insulin resistant patients as compared to non insulin resistant patients but it was found to be statistically insignificant.

The prevalence of hyperinsulinemia and insulin resistance in patients with hypertension alone was 43.33% & 48.33% respectively, in hypertension+obesity it was 64.51% & 70.97% respectively, in hypertension+ dyslipidemia it was 64.86% & 62.16% respectively and in hypertension+obesity+ dyslipidemia it was 79.16% & 79.16% respectively. Thus the hyperinsulinemia & the insulin resistance was increasing with the addition of risk factors.

DISCUSSION

In the present study, amongst 60 cases in study group, 27 (45 %) were males and 33 (55 %) were females. Amongst 20 cases in control group 9 (45 %) were males and 11 (55 %) were females. In the study group the ratio of male patients to female patients was 1:1.22. (Table 1)

In our study group the number of patients in different age group <40, 41-50, 51-60, 61-70 and > 70 yrs were 5, 20, 24, 9 and 2 respectively with a percentage of 8.33%, 33.33%, 40%, 15% and 3.33%. The maximum number of patients were in age group 51-60 and the next higher numbers of patients were in the age group 41-50 yrs. Minimum number were in age group >70 yrs

Analysis of Serum Insulin Levels/insulin resistance and Fasting Blood Sugar in study & control group

In the present study mean **serum insulin level** among the study group was significantly more than the control group (p = 0.0143). The **mean fasting blood sugar level** among the study group was significantly more than the control group (p=0.0001). (Table No.-1)

In a Indian study at delhi, by Jhamb R et al, 2005 mean fasting glucose in hypertensive patients was 96.11 \pm 9.6 mg/dl which was significantly high as compared to 83.125 \pm 10.062 mg/dl in normal healthy controls.(p=0.033). The mean fasting serum insulin level in hypertensive patients was 14.82 \pm 13.27 μ U/mL which was significantly high as compared to 6.48 \pm 6.45 μ U/mL in normal healthy controls.(p<0.001). In a study on patients with essential hypertension by Lima NKC et al, 2009 the mean fasting glucose was 95 \pm 11 mg/dl, the mean fasting insulin was 14 \pm 7 μ U/mL.

Thus the result of our study was in accordance with this study.

Spangler JG et al, 1998 in a study on 140 patients with essential hypertension commented the Mean fasting glucose was 103 \pm 12 mg/dl and the mean fasting serum insulin level was 17.1 \pm 10.6 μ U/mL which is slightly higher than our study may be due to the fact that only the patients with BP >160/90 were selected as cases.

In our study hyperinsulinemia among the patients with hypertension was observed in 43.33% patients, which is highly significantly more than the control as none of the patient in control group had hyperinsulinemia. Hyperinsulinemia was found to be slightly more prevalent in female patients (45.45%) as compared to males (40.74%) but on statistical analysis this difference was not significant.

In the present study the mean HOMA-IR level among the study group was significantly more than the control group (p=0.011). (Table No. 1). In an Indian study Deepa R et al 2004, commented that Prevalence of hypertension increased with an increase in quartiles of fasting insulin levels (p=0.035) and HOMA IR (p=0.03). Logistic regression analysis revealed that HOMA IR was significantly associated with hypertension. Jhamb R et al, 2005 in the study observed the mean HOMA-IR level in hypertensive patients was 3.568 \pm 3.34 mmol/l. μ U/mL which was significantly high as compared to 1.45 \pm 1.34 mmol/l. μ U/mL in normal healthy controls.(p<0.001).

Thus the result of our study was in accordance with this study.

In our study, insulin resistance among the patients with hypertension was observed in 48.33% patients, which is **highly significantly more** than the control as none of the patient in control group had insulin resistance. Insulin resistance was found to be

slightly more prevalent in female patients (51.51%) as compared to males (44.44%) but on statistical analysis this difference was not significant.

Analysis of lipid profile in study & control group

In the present study the lipid profile was found to be more deranged in study group as compared to control group. The mean serum cholesterol in study group was more than control group (p=0.196). The mean serum triglyceride in study group was significantly more than control group (p = 0.007). The mean serum HDL was low in study group than control group (p = 0.086). The mean serum LDL was more in study group than control group (p = 0.155). (Table No. 1) Zavaroni I et al, 1992 reported that, patients with hypertension had significantly higher plasma TG concentration as compared to normal subjects (P less than 0.05). They also commented that the patients with hypertension and hyperinsulinaemia were also glucose intolerant and dyslipidaemic. Spangler JG et al, 1998 in a study on patients with essential hypertension obtained a mean cholesterol value of 219±43 mg/dL, mean LDL =138±37 mg/dL, mean HDL 51±14 mg/dL and mean triglyceride=148±80 mg/dL. In a study on patients with essential hypertension by Lima NKC et al, 2009 the mean total cholesterol was 205±39 mg/dl, mean LDL-cholesterol was 128±35 mg/dl, mean HDL was 46±12 mg/dl, mean triglyceride was 152±71 mg/dl. In the same study the 51% of patients had serum cholesterol>200 mg/dl, 38% had serum LDL cholesterol, 46% had abnormal HDL and 48% had serum triglyceride>150mg/dl. This slightly higher lipid profile derangement as compared to our study may be due to variations in life style, race, ethnic background, culture and genetic susceptibility as this is a study from outside India.

Analysis of strength of association of various risk factors with insulin level/ insulin resistance

In our study the prevalence of hyperinsulinemia in patients with hypertension alone 43.33%, hypertension+obesity it was 64.51%, hypertension+ dyslipidemia it was 64.86%, hypertension+obesity+dyslipidemia it was 79.16%. Thus in the present study the hyperinsulinemia was increasing with the addition of risk factors. The prevalence of insulin resistance in patients with hypertension alone 48.33%, hypertension+obesity it was 70.97%, hypertension+dyslipidemia it was 62.16%, hypertension+obesity+dyslipidemia it was 79.16%. Thus in the present study the insulin resistance was increasing with the addition of risk factors. (Table No. 3) On statistical analysis the prevalence of hyperinsulinemia and insulin resistance was significantly high among the patients with HTN+obesity+Dyslipidemia as compared to the patients with HTN alone. (p=<0.05). (Table No.3)

In a study by Spangler JG et al, 1998 mean fasting insulin levels by patient category reveal an increasing trend with the addition of risk factors to pure hypertension. These insulin levels are 13.7±8.6 µU/mL for patients with hypertension alone; 17.3±11.2 µU/mL for patients with hypertension plus obesity; 17.4±8.9 µU/mL for patients with hypertension plus hyperlipidemia; and 20.8±10.9 µU/mL for patients with all 3 conditions (p=0.03). The addition of abdominal obesity to pure hypertension (the referent category) more than doubled the risk for an elevated fasting insulin level (AOR, 2.69; 95% CI, 1.04-6.89). While not statistically significant, the addition of hyperlipidemia to hypertension also more than doubled the risk for an elevated insulin level. In an additive fashion, both factors combined with hypertension increased the risk of an elevated insulin level by 5-fold (AOR, 5.11; 95% CI, 1.59-16.4). Spangler JG et al, 1998 observed increasing values of hyperinsulinemia & insulin resistance with clustering of risk factors, this observation is in accordance with our observation.

Hence this study clearly reemphasizes the need to initiate intensive efforts aimed to improve insulin sensitivity and treating all of the CVD risk factors in patients with essential hypertension, not just the blood pressure.

TABLES

Table No 1

Group/ Serum Insulin	Study group (n=60)	Control group (n=20)	t value	P value
Fasting Mean Serum Insulin (µU/mL ± SD)	14.90±13.27	7.31±4.20	2.506	0.0143
Mean Fasting Blood Sugar	95.70±12.29	82.55±8.46	4.438	0.0001
S. Cholesterol (mg/dl)	186.7±41.13	174.1±22.45	1.303	0.196
S.Triglycerides (mg/dl)	153.21±55.68	117.55±28.49	2.738	0.007
S. HDL (mg/dl)	46.35±7.80	49.7±6.30	1.738	0.086
S. LDL (mg/dl)	121.78±42	107.5±24.78	1.435	0.155
Mean BMI (kg/ m2)	25.19±4.04	23.20±2.72	2.04	0.044

Table No-2

Group	Risk factors	Number of Patients	Hyperinsulinemia No. (%)	Insulin Resistance No. (%)
I	HTN	60	26 (43.33%)	29(48.33%)
II	HTN+Obesity	31	20 (64.51%)	22(70.97%)
III	HTN+Dyslipidemia	37	24 (64.86%)	23(62.16%)
IV	HTN+Obesity+Dyslipidemia	24	19 (79.16%)	19(79.16%)

LEGENDS

Table 1 :- COMPARISON OF VARIOUS RISK FACTORS AMONG THE STUDY AND CONTROL GROUP

Table 2 :- ASSOCIATION OF HYPERINSULINEMIA AND INSULIN RESISTANCE WITH RISK FACTORS AMONG PATIENTS WITH ESSENTIAL HYPERTENSION

REFERENCES

- 1) Spangler JG, Bell RA, Summerson JH, Konen JC. Hyperinsulinemia in Hypertension (Associations with Race, Abdominal Obesity, and Hyperlipidemia). Arch Fam Med. 1998;7:53-56
- 2) Edelson GW, Sowers JR. Insulin resistance in hypertension: a focused review. Am J Med Sci 1993;306:345-7.
- 3) Weidmann P, Müller-Wieland D, de Courten M, Krone W. Insulin resistance and arterial hypertension. Herz. 1995 Feb;20(1):16-32.
- 4) Ferrannini E. Insulin and Blood Pressure (Connected on a Circumference?). Hypertension. 2005;45:347
- 5) Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C and Stern MP. Identification of Individuals With Insulin Resistance Using Routine Clinical Measurements. Diabetes 2005;54:333-39
- 6) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF and Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.
- 7) Jhamb R, Gaiha M, Chakravarti AL, Daga MK. Insulin Resistance/Hyperinsulinaemia as a Risk Factor for Common Carotid Artery Intima Media Thickness in Essential Hypertension. JIACM 2005;6(2):122-8
- 8) Lima NKC, Abbasi F, Lamendola C and Reaven GM. Prevalence of Insulin Resistance and Related Risk Factors for Cardiovascular Disease in Patients With Essential Hypertension. Am J Hypertens 2009;22:106-111
- 9) Deepa R, Pradeepa R, Shanthirani C, Mohan V. Association of hypertension with cluster of insulin resistance syndrome factors: the Chennai Urban Population Study (CUPS-12). Acta Diabetologica 2004;41(2):49-55.
- 10) Zavaroni I, Mazza S, Dall'Aglio E, Gasparini P, Passeri M, Reaven GM. Prevalence of hyperinsulinaemia in patients with high blood pressure. J Intern Med. 1992;231(3):235-40