HYPERTENSION DUE TO INSULIN RESISTANCE IN NON DIABETICS

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Abstract- Diminished tissue sensitivity to insulin is a characteristic of various pathological conditions termed the insulin resistance syndrome, also known as the metabolic syndrome or cardio metabolic syndrome . The metabolic syndrome is not a single disease, but rather a complex cluster of symptoms that include a large waist circumference, hypertension, hyperglycemia, dyslipidemia and insulin resistance, all of which are commonly associated with increased risk of obesity and Hypertension, which is treatment resistant. Since patients with metabolic syndrome are commonly afflicted with cardiovascular morbidities, the metabolic syndrome and cardiovascular diseases share common pathways including increased oxidative stress, defective glucose, lipid metabolism, low grade inflammation, hypercoagulability and endothelial damage. Previously, investigators proposed to use the “circulatory syndrome” to refine the metabolic syndrome concept through the addition of markers of cardiovascular diseases such as renal impairment, microalbuminuria, arterial stiffness and left ventricular dysfunction. It has become increasingly obvious that insulin resistance and the efforts made by the insulin-targeted organs to compensate for this defect play a vital role in the pathogenesis and clinical course of the metabolic syndrome .Insulin resistance along with normal glucose tolerance capacity couples with fulminating cases of hypertension. Indian population is specially prone to this very problem. This case –control study collected and analyzed data regarding the coexistence of Hyperinsulinemia and Hypertension. A significant differences in terms of Lipid Profile , Blood Pressure , obesity and BMI was observed among Insulin Resistance subjects and controls with normal Insulin levels.

Key Words- Hyperinsulenemia, Blood Pressure , Lipid Profile, Waist Circumference , BMI

Introduction- Hypertension is defined as the sustained elevation of either or both systolic and diastolic blood pressure while at rest. There are several different classifications of hypertension, but the two main categories are primary, also called essential hypertension, and secondary hypertension. The majority of all those diagnosed with hypertension fall under the primary category while only a small percentage are classified as secondary hypertensive. Secondary hypertension is the result of some other condition or disease where as primary Hypertension is said, by conventional medicine, to have no identifiable cause for development. The pancreas tries to correct this by massively increasing insulin production, which leaves high levels of serum insulin that are not utilized. One of the many effects of this over production is the increased re-absorption of sodium by the kidneys.[vi] This causes increased extracellular fluid volume, which will demand greater cardiac output and raise blood pressure. There are also several other pathways in which sustained elevated levels of insulin can stimulate the sympathetic nervous system and increase peripheral vascular resistance and raise blood pressure. Hyperinsulinemia can also be caused by the uses of injected insulin. The hyperbolized

amount of injected insulin needed to eventually make its way to the vascular system can increase insulin resistance. In spite of its extremely limited benefit, large doses of insulin are sometimes used in Type II patients in an attempt to overcome insulin resistance and restore normoglycemia, however this may be just adding to a hyperinsulinemia problem. Another link to cardiovascular problems that can affect diabetes patients and the general population is serum homocysteine levels. Over three decades ago a Dr. Kilmer McCully, a Harvard educated researcher, discovered that high levels of serum homocysteine were a direct link to heart disease. Cholesterol occlusion can be the end result of a process that first begins damage to the intima lining of the vessel due to an inability to repair it from vitamin deficiencies. This damage causes vascular seepage and the body, without raw materials to effect proper repair, mobilizes fibrin and cholesterol to construct a patch and as long as the vitamin deficiency exists cholesterol keeps being produced. Some studies clearly demonstrate the direct correlation between a decrease in insulin doses and a corresponding drop in blood pressure without deterioration in glucose control.

Many epidemiological and clinical studies have shown that Hyperinsulinemia and Insulin resistance have a key role in any metabolic diseases such as Diabetes, Hypertension , Dislipidemias , Ischaemic heart diseases. Many previous studies have described that Hyperinsulinemia in normoglycaemic patients with hypertension and suggested that these patients could be Insulin resistant. . Later many more studies proved that lean hypertensive patients had lower insulin mediated glucose clearance (disposal0 than normal controls. Although many studies have proved this relationship but some results are inconsistent and still the relationship between Hyper Insulin level and High Blood Pressure is controversial. Thus this study is designed to detect the prevalence of Hyperinsualenemia with essential and treatment resistant hypertension without Diabetes and Ischaemic heart disease.

Material & Methods- this is a cross sectional study. The hypertensive patients are selected randomly by contacting in Hospitals in Bilaspur and Raipur . The subjects were randomly screened and by fulfilling the inclusion and exclusion criteria, they were finally selected. The inclusion criteria was presence of essential and treatment resistant hypertension and age above 20 years .The BP should be more than 145/100 mm of Hg. The hypertensive subjects who had hyperglycaemia with frank diabetes were excluded from the study. [Patients with Fasting blood Glucose > 130 mg/dl, Postprandial Blood glucose > 180-200 mg/dl and impaired glucose tolerance >130 mg/dl . The healthy controls were picked up randomly from the society, who were demographically matched with the subjects, but without having Hypertension, Diabetes, Impaired Glucose tolerance , Impaired fasting glucose .

Blood Collection-After taking written consent and completing ethical formalities ,epidemiological data was collected from every subject and control. For estimation of fasting blood glucose level the blood sample of 10 ml was withdrawn 10 hours after taking meal. This sample was also used to assess the fasting total lipid profile level and fasting serum Insulin level. For estimation of total lipid profile the following method was adopted-

Objectives- The following objectives were drawn to perform this work-

1] Estimation of Serum Insulin level –Fasting and Postprandial in both groups

2] Estimation of Serum Glucose level in both groups

3] Estimation of total Lipid profile level including Cholesterol, Triglyceride, HDL and LDL in both groups

4] Estimation of BMI in both groups

5] Estimation of Weight, Waist circumference

ESTIMATION OF TOTAL LIPID PROFILE –

OPTICAL MEASUREMENTS - All routine colorimetric estimations were performed on Spectro-colorimeter 103 and Spectro-photometer 106, and Colorimeter 114, (5-filters) (Systronics, India).

BLOOD COLLECTION - Blood sample (2 ml) was collected from the control and experimental group. Blood samples were collected preferably before meals. All analytics were done on serum and not on plasma, as EDTA interferes with lipid estimation procedures particularly with high density lipoprotein (HDL). Apart from blood collection and estimation done in the lab, the reports of lipid profile analysis were done in the collaboration with Aakash Patho-Lab, Bilaspur and also from Abhay Tamrakar, Pathologist, Bilaspur, from City Hospital, Bilaspur; The Reports were also collected from the Bose Pathological Lab Bilaspur. The Blood samples were stored in cold temperature (4° C) before estimation, if necessary, but were discarded after 8 hours. They were equilibrated to room temperature before estimation. Data pertaining to lipid profiles of normo-tensive controls, they were served as collected data.(19 controls) Rests of them were analyzed, but as they were in general agreements, so the collected and analyzed data were taken as a whole.

ISOLATION OF SERUM-The blood samples obtained were stored at room temperature and then centrifuged at 4° to 8°C for 6 to 8 min at 3500 rpm to remove serum from the blood.

ESTIMATION OF TOTAL CHOLESTEROL (mg/100 ml)- Cholesterol in the blood sample was determined by the one step procedure of Wybenga and Plleggi (Catalog no-25924).This procedure is based on the oxidation of Cholesterol to Cholesterol Oxidase (CHO).This is again oxidized to Cholest 4-en 3-one and Hydrogen Peroxide. Hydrogen peroxide formed reacts with 4-amino antipyrine and 4-chlorophenol in the presence of peroxide (POD) to produce pink colored quinonemine dye. The intensity of the color produced is proportional to the cholesterol concentration in the sample. Briefly the assay comprises of the following reactions-

CE

Cholesterol Esterase---------------> Cholesterol + Fatty Acid

CHOD

Cholesterol +O2---------------------> Choleste-4-en-3 one+ H_2O_2

POD

H_2O_2+ 4-AAP + 4- Chlorophenol---------->Quinoneimine + H_2O

(Coloured Dye)

Protocol- Reagent 1 - Cholesterol reagent.

Reagent 2 - Standard Cholesterol.

Serum, 0.25 ml and cholesterol reagent 5.00 ml were mixed in a test tube thoroughly and then kept in boiling water bath for 90 seconds. The tube was subsequently cooled to room temperature under running tap water. The optical density (O.D) of the test sample was read using a Spectrophotometer at 560 nm. Standard cholesterol solution was prepared by using 0.25 ml of standard cholesterol solution and was mixed with 5.0 ml of cholesterol reagent and carried through the same steps as applied to serum samples. A blank solution was prepared by using 5.00 ml cholesterol reagent in test tube and carrying the subsequent steps as above. Absorbance of the cholesterol standard and serum samples were then read at 560 nm against the blank. All the reagents of the kit are stable at 2-8°C. As the reagent 1–Cholesterol reagent is corrosive, so mouth pipetting was avoided.

Linearity- This assay was linear up to 600-mg/100 ml cholesterol value.

ESTIMATION OF HIGH DENSITY LIPOPROTEIN (HDL) mg/100 ml- HDL in the blood/serum samples was determined by the procedure of Gorden et al (1977). The procedure is based on the principle of production of Hydrogen Peroxide, which finally gives blue color. The optical Density of the developed color is measured at 600 nm, which is proportional to the HDL in the test sample.For the estimation of HDL mg (%) the diagnostic Kit of Span Diagnostics Ltd was used (Catalog No. 25924) based on the one step method of Wybenga and Plleggi. The principle behind the process is that Anti-human β Lipo-protein Ig in reagent A binds to lipoproteins (LDL, VLDL and Chylomicrons) other than HDL. This immuno-complex blocks cholesterol other than HDL. When reagent B is added, only HDL Cholesterol reacts with enzymatic chain (CHE-CO).Hydrogen Peroxide produced by enzymatic reaction yields a blue color complex upon oxidative condensation with F-DAOS and 4-APP in presence of peroxidase, whose absorbance is read at 600 nm, proportional to HDL Cholesterol concentration in the sample.

PROTOCOL-For the estimation, 0.3 ml of fresh/stored serum was used. Firstly, the serum test samples were mixed with 0.3 ml precipitating reagent (Polyethylene Glycol 16%, Additives and Stabilizers). This is used to precipitate Lipo-proteins-LDL and VLDL. Both are mixed well and then kept at room temperature for about 10 minuets. After this, the solution was centrifuged at 2000 rpm for 15 minutes. From this 0.2 ml clear supernatant was taken and 5.0 ml Cholesterol Reagent was added to it. The contents were mixed well and then the tube was kept immediately in the boiling water bath for 90 seconds and cooled immediately to room temperature under running tap water. The optical density was read on a spectrophotometer at 600 nm. The same procedure was applied for preparing standard solution. The developed color was stable at least 10 minutes. It was kept away from strong light sources.

Linearity - This assay was linear up to 400 mg/100 ml levels.

ESTIMATION OF TRIGLYCERIDE (TG) mg/100 ml-Triglycerides in the blood/serum samples were determined by the procedure of Bucolo David (1973). The procedure is based on the principal of production of red colored dye, Quinoneimine, which absorbs sharply at 510 nm. Briefly the assay comprises to the following reactions-

Lipase (serum/microbial)

1) Triglyceride------------------------>Glycerol + Fatty Acids

Glycerol Kinase

2) Glycerol +ATP------------------>Glycerol 3- phosphate + ADP

Glycerol Phosphate Oxidase

3) Glycerol-3-phosphate+O_2---->Dihydroxy acetone phosphate+ H_2O_2

Peroxidase

4) H_2O_2+4-AAP+4-chlorophenol------------->Quinoneimine+H_2O

(Colored Dye)

For the estimation of Triglyceride (mg/100 ml) the diagnostic kit of Chema diagnostics Ltd Glaxo– was used which was azide free (catalog No. 77034) (6× 250 ml) was used. Triglycerides in the samples are hydrolyzed by microbial lipases to glycerol and free fatty acids (FFA). Glycerol is phosphorylated by Adenosine 5-triphosphate (ATP) to glycerol -3-phosphate (G-3-P) in a reaction catalyzed by glycerol-kinase (GK).G-3-P is oxidized to dihydroxy-acetone phosphate (DAP) in a reaction catalyzed by the enzyme glycerol phosphate oxidase (GOP).In this reaction hydrogen peroxide (H_2O_2) is produced in equimolar concentration by the level of triglyceride present in the sample.H_2O_2 reacts with 4-Amino-antipyrine (4-AAP) and 4-chlorophenol, in a reaction catalyzed by peroxidase (POD).The result of this oxidative coupling is Quinoneimine, a red colored dye. The absorbance of this dye in solution is proportional to the concentration of triglycerides in the sample. The reagents of the kit were supplied already in liquid, ready to use form. The kit for in vitro diagnosis was used.

PROTOCOL- Serum, 0.02 ml was mixed with 2 ml reagent. Both were mixed well and incubate at 37°C for 5-8 min. The optical density was read at 510 nm in spectrophotometer. The same procedure was carried out for preparing standard solution. The absorbance of test and standard solutions were read at 510 nm against blank reagent.

Linearity – This assay was linear at least to 1000 mg/100 ml Triglyceride value.

CALCULATIONS-

The following formula was used to determine the mg/100 ml value of the following-

(A) TOTAL CHOLESTEROL-

(Normal level -130-250 mg/100 ml in adults)

$$\text{Serum Cholesterol (mg/100 ml)} = \frac{\text{Optical density of Test (Ax)}}{\text{Optical density of Standard (As)}} \times 200$$

(B) HIGH DENSITY LIPO-PROTEIN (HDL)-

(Normal level - 35-75-mg/100 ml for adult female)

$$\text{HDL (mg/100 ml)} = \frac{\text{Optical density of Test}}{\text{Optical density of standard}} \times 50$$

(C) ESTIMATION OF TRIGLYCERIDE (TG)-

(Normal level = 10-190 mg /100 ml for adult woman)

$$TG\ (mg/100\ ml) = \frac{\text{Optical density of test}}{\text{Optical density of standard}} \times 200$$

(D) CALCULATION OF LOW-DENSITY LIPOPROTEIN (LDL mg /100 ML)

For this the **fw** formula was adopted =

(Normal Range = 30-60 mg/100 ml)

(A) Triglyceride mg/100 ml = **x**

(B) **X** + HDL mg/100 ml = **y**

(C) Total cholesterol –**y** = **LDL** (mg /100 ml)

ESTIMATION OF SERUM INSULIN LEVELS- For estimation of serum Insulin levels Serum c- peptide level was used for maximum patients and for some patients ELIZA kit of Insulin MONOBIND Inc (product code 2425-300) was used .Mini Viadas 100 was used for the estimation. For some sample the Insulin was indirectly estimated by C-Peptide method.

ESTIMATION OF BLOOD PRESSURE- By the use of Auscultators the Blood pressure was measured of each subject and control. The BP of participants was measured for one week and the mean values were taken into consideration.

STATISTICAL METHODS USED IN THE ANALYSIS OF DATA-For statistical analysis of data the package SPSS-STAT was used. Mean, Standard Deviation, Degree of Correlation-all are calculated by using this package, butt Value –Level Of Significance was manually calculated on the basis of two sample means by using the formula-

$$S = \frac{(m_1)^2 + (m_2)^2}{\sqrt{n_1 + n_2 - 2}}$$

$$t = \frac{(m_1)^2 - (m_2)^2}{S} \times \frac{\sqrt{n_1 \times n_2}}{n_1 + n_2}$$

OBSERVATIONS-Total 78 patients with hypertension were included after following the inclusion and exclusion criteria. Also 78 healthy controls were included in the study who were demographically matched with the subjects. The mean fasting Insulin level was estimated as an average of 30.15 ± 4.08 μ IU /ml in Hypertensive group and the level of Insulin as estimated in control group was 11.34 ± 1.019 μ IU /ml . This is also statistically significant difference ( ) .The mean fasting Insulin serum level was significantly higher in nonveg eaters of hypertensive group and even comparatively higher in nonveg eaters of control groups. The weight , the waist circumference and BMI were higher in Hyperinsulinemic group. (BMI Subjects- 24.23 ± 4.09 and 20.13 ± 0.09 in control group.). Mean waist circumference in Hypertensive group was 98.67 ± 1.34 and in control group was 89.23 ± 1.33 .

TABLE-1 ESTIMATED PARAMETERS-

Sr No	Parameters	Subjects (78)	Controls(78)	T value
A.	Age mean	57.23 ± 2.78	56.45 ± 1.67	0.0789*,**
B.	Sex	34F / 44 M	31F /	---
C.	weight	66.43 ± 2.09	62.12 ± 3.51	1.06*,**
D.	BMI	24.23 ± 4.09	20.13 ± 0.09	1.34*,**
E.	Waist Circumference	98.67 ± 1.34	89.23 ± 1.33	0.932*,**
F.	Fasting Glucose Level	98 ± 3.11	101 ± 1.09	0.0086*,**
G.	Postprandial Glucose level	122 ± 0.53	119 ± 1.03	0.4712*,**
H.	Fasting Insulin Level	30.15 ± 4.08 μ IU /ml	11.34 ± 1.019 μ IU /ml	5.529*,**
I.	Postprandial Insulin level	41.02 ±2.31 μ IU /ml	13.02 ± 1.33 μ IU /ml	3.40*,**
J.	Serum Cholesterol Level	1.89±0.17 mg/dl	1.19±0.12 mg/dl	2.42*,**
K.	Serum Triglyceride level	1.91±0.42 mg/dl	1.51±0.32 mg/dl	4.05*,**
L.	Serum HDL level	0.28±0.02 mg/dl	0.38±0.02 mg/dl	1.129*,**
M.	Serum LDL level	1.23±0.16 mg/dl	0.53±0.16 mg/dl	5.08*,**
N.	Blood Pressure	109/233	93/153	----

*P<0.05 level, **P<0.01 level. SD Values showed in parenthesis.

TABLE-2 THE COMPOSITION OF LIPID PROFILE OF CONTROLS-

Age Group	No. of Participants	Total Cholesterol	Triglyceride	HDL	LDL
37-40	9	1.12±0.33	0.82±0.24	0.51±0.10	0.45±0.14
41-44	14	1.23±0.12	0.84±0.23	0.52±0.07	0.54±0.13
45-48	10	1.32±0.14	1.16±0.34	0.49±0.08	0.60±0.10
49-52	24	1.18±0.18	0.75±0.35	0.52±0.09	0.52±0.12

53-56	15	1.35±0.25	1.30±0.28	0.49±0.10	0.53±0.13
57-60	6	1.30±0.22	1.03±0.43	0.52±0.10	0.58±0.25
60+	4	1.19±0.12	1.51±0.32	0.38±0.02	0.53±0.16

n = 78 (Values expressed as $\bar{x}$ mg.ml^{-1} serum and are presented as Mean value ± Standard Deviation).

TABLE-3 THE COMPOSITION OF LIPID PROFILE OF SUBJECTS-

Age group	No. of Participants	Total Cholesterol	Triglyceride	HDL	LDL
37-40	12	2.02±0.33	0.95±0.29	0.29±0.06	1.46±0.24
41-44	11	2.07±0.25	1.63±0.38	0.27±0.08	1.49±0.19
45-48	12	1.50±0.35	1.11±0.39	0.31±0.07	0.98±0.31
49-52	9	1.83±0.26	1.24±0.37	0.30±0.09	1.29±0.22
53-56	22	1.88±0.25	1.87±0.28	0.34±0.07	1.17±0.19
57-60	10	1.76±0.22	1.76±0.46	0.27±0.05	1.13±0.17
60+	4	1.89±0.17	1.91±0.42	0.28±0.02	1.23±0.16

n = 78 (Values expressed as $\bar{x}$ mg.ml^{-1} serum and are presented as Mean value ± Standard Deviation).

TABLE-4 THE STATISTICS OF THE LIPID PROFILE OF BOTH THE GROUPS-

Factors Of Lipid Profile	(mean ± Sd)		Change in percent-age value	(df = 154) t value
	controls (n=78)	subjects (n=78)		
Cholesterol(mg/ml)	1.25 (±0.08)	1.85 (±0.17)	↑ 48%	17.63*,**
Triglyceride(mg/ml)	0.98 (±0.20)	1.49 (±0.36)	↑ 53%	18.68*,**
HDL (mg/ml)	0.59 (±0.18)	0.29 (±0.02)	↓ 51%	24.29,*,**
LDL (mg/ml)	0.54 (±0.16)	1.26 (±0.17)	↑ 131%	49.00,*,**

*P<0.05 level, **P<0.01 level. SD Values showed in parenthesis.

DISCUSSION- Insulin resistance may be linked to many metabolic disorders like dislipidemias, coronary disorders, High Blood Pressure and Diabetes Mellitus some abnormalities are also related to this as obesity. The association of resultant obesity and dislipidemias increases cardiac mortality and morbidity in Insulin Resistant persons. Many previous studies proved that Insulin Resistant developed well before the development of frank symptoms shows the presence of Hyper Insulaenemia, thus detection and identification of this very condition has great prognostic value at the earliest possible way. This Serum Insulin level is generally estimated by euglycaemic insulin clump technique, but due to it's complexity it is not available for clinical purposes. Measuring fasting plasma Insulin level is more common but it is less accurate. Both fasting and postprandial Insulin levels are high in affected persons. Some India based studies showed that up to 15 % Indian are affected by Insulin Resistance condition.

In the present study 63.54% hypertensive subjects had Hyperinsulinemia , but only 19.12 % controls had marginally fasting higher serum Insulin levels. The controls showed normal glucose tolerance ,also surprisingly the subjects having Hyperinsulinemia and high BP , 59.34 % of them showed normal glucose tolerance . The subjects showed significant dislipidemias as compared to controls, this may be Hyperinsulinemia driven. And may be root cause of treatment resistant High Bolld Pressure in subjects.

CONCLUSION- Insulin resistance and hypertension are considered as prototypical "diseases of civilization" that are manifested in the modern environment as plentiful food and sedentary life. The human propensity for insulin resistance and hypertension is a product, at least in part, of our evolutionary history. Adaptation to ancient lifestyle characterized by a low sodium, low-calorie food supply and physical stress to injury response has driven our evolution to shape and preserve a thrifty genotype, which is favorite with energy-saving and sodium conservation. As our civilization evolved, a sedentary lifestyle and sodium- and energy-rich diet, the thrifty genotype is no longer advantageous, and may be maladaptive to disease phenotype, such as hypertension, obesity and insulin resistance syndrome. This article reviews human evolution and the impact of the modern environment on hypertension and insulin resistance. Abundant clinical and epidemiologic evidences demonstrate a close linkage between insulin resistance and hypertension. The coexistence of insulin resistance and hypertension results in a substantial increase in the risk of developing cardiovascular disease and type II diabetes. Underlying the mechanisms is complex and may involve a low grade chronic inflammation and oxidative stress. As humans evolve, the thrifty genotype for high cytokine responder (eradication of injury), mild insulin resistance (protection against starvation), or sodium preservation (maintenance of body fluid),which favored our ancestors, aiding them in the survival of critical conditions such as famine, infection, trauma and physical stressors, may be positively selected, which may be maladaptive to our current, modern lifestyle, resulting in insulin resistance, hypertension, type II diabetes and cardiovascular diseases .

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