Glucose Tolerance & Insulin Response in Patients with Hypertension

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Abstracts: Background: Insulin resistance leads to impaired glucose tolerance, dyslipidemia, and other adverse cardiovascular effects. Euglycemic insulin clamp have shown that essential hypertension per se is a state of insulin resistance and has been associated with an increased incidence of diabetes Aims: To ascertain the prevalence of several degrees of glucose abnormalities in patients with hypertension and to examine the insulin secretory response to oral glucose load. Study design, Material and Method: This cross-sectional analytical study included 325 hypertensive patients (with or without diabetes)and 100 control subjects. An oral glucose tolerance test (OGTT) following WHO guidelines was performed in all subjects, with measurement of insulin at baseline and every 30 minutes after the glucose load. Results: Abnormal glucose metabolism was observed in 70.77% of patients (95% confidence interval [CI], 65.87% - 74.21%). Of the 325 patients, 29.23% patients showed normal glucose metabolism. Impaired glucose tolerance (IGT) and Impaired fasting glycemia (IFG) were diagnosed in 30.46% and 16.61% patients respectively .Total diabetic population in the hypertensive patients were 23.69% (silent previously undiagnosed diabetes mellitus was diagnosed in 9.53% of patients while 14.15%reported a previous diagnosis of diabetes mellitus).Decreasing glucose tolerance was associated with insulin resistance. From normal glucose tolerance condition through IGT, IFG to diabetic, the HOMA IR progressively increased. Results of standard OGTT and corresponding insulin response after 0, 30, 60 and 120 minutes were significantly higher in patients compared with control subjects. LVMI and severity of glucose intolerance were significantly related. Male gender, higher levels of insulin (fasting insulin/HOMA IR) and greater adiposity (BMI) were all strongly associated with the severity of glucose abnormalities. Prevalence of metabolic syndrome increased progressively with severity of glucose abnormality. Conclusions: More than two-third of the hypertensive patients exhibited different glucose abnormalities and exaggerated insulin response to glucose load (hyperinsulinemia) along with cluster of other cardiovascular risk factors, whose prevalence increases with severity of glucose intolerance.[Parchwani D et al NJIRM 2011; 2(4) : 83-90]

Key Words: Glucose tolerance, Hypertension, Insulin, Insulin resistance

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Introduction: Type 2 diabetes mellitus (Type 2 DM) is a disease of common occurrence and a wealth of evidence suggest that by the time type 2 DM is developed, appreciable β cell destruction have already occurred[1], due to insulin resistance which have existed long before the onset of overt hyperglycemia. Physiological studies (euglycemic insulin clamp) have shown that essential hypertension per se is a state of insulin resistance[2]. Insulin resistance leads to impaired glucose tolerance, lowered insulin sensitivity and several studies have documented the prevalence of type 2 DM among hypertensive patients with substantial variability[3,4]. In addition, both hypertension and insulin resistance have been associated with left ventricular hypertrophy (LVH), and it has been suggested that abnormal glucose metabolism accelerates the development of LVH[5] thereby increasing the risk of future cardiovascular morbidity and mortality. Thus in hypertensive patients, early diagnosis and treatment of an abnormal glucose metabolism may be particularly important to reduce cardiovascular disease.

Despite the degree of interest shown in the subject, only recently has there been greater focus on the underlying pathophysiology and glucose metabolism, but very few attempts has been made to determine the impaired glucose tolerance and diabetes prevalence in patients with hypertension. A better understanding of this may influence the nature of therapeutic intervention in hypertensive patients with or even before development of type 2 DM and cardiovascular impairment. Thus in present study an attempt has been made to ascertain the prevalence of several degrees of

glucose abnormalities in patients with hypertension and to examine the insulin secretory response to oral glucose load to test whether hypertension is associated with insulin resistance.

Material and Methods: This study was designed to determine the prevalence of glucose abnormalities in hypertensive patients and to examine the insulin secretory response to oral glucose load. 425 subjects with either sex (254 males and 171 females) of varying age (range: 33.5 – 65.7 years) were enrolled from November 2009 to August 2010 and were categorized into two main groups which include:

GROUP I : Healthy controls i.e. subjects not suffering from diabetes, nor having any family history of diabetes, not suffering from hypertension or from any acute or chronic disease , nor taking any drugs believed to alter plasma glucose level. n = 100 (50 males and 50 females)

GROUP II : Hypertensive patients [Based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII)[6], and those who had used BP lowering medications] n = 325 (204 males and 121 females)

Exclusion criteria were:

- Patients who needed continuous or periodic use of corticosteroids.
- Patients who visited the pregnancy clinic or who had given birth within the preceding six weeks.
- Lack of approval by physician for whatever reason(s).
- Subjects showing disinterest.

All subjects were studied as outpatient. Participant's examination included interviews for medical and nutritional history. Present and past history of each case was recorded in detail regarding their general information i.e. name, age, sex, address, religion, occupation, economic status, nutritional and personal habits, education, medication and history suggestive of any systemic illness. Each subject was then examined for various anthropometric parameters: Weight (Kg) and height (meters were measured (using Omron digital body weight scale HN-286 and SECA 206 wall mounted metal tapes respectively). Body Mass Index (BMI) was calculated by Weight (Kg) / height squared (m^2). Waist circumference was assessed in the standing position, midway between the highest point of the iliac crest and the lowest point of the costal margin in the mid-axillary line. Hip circumference was measured at the level of the femoral greater trochanter. All anthropomorphic measures reflect the average of 2 measurements (measured by same person on same instrument to avoid inter-instrument and inter personal variation). Blood pressure (BP) was measured two times in the seated position after 10 minutes of rest with a standard manual mercury sphygmomanometer (Diamond). The recorded pressure of the two measurements was averaged. Subjects with a systolic and diastolic BP equal to or exceeding 140/90 mmHg, and those who had used BP lowering medications were considered to have hypertension. Age was defined as the age at the time of interview (though no documentary proof had been entertained) and the date of diagnosis of hypertension was obtained from the patient. A 12 - lead electrocardiogram was performed in hypertensive patients. Two-dimensional-guided M-mode echocardiograms were performed with the patients lying in left lateral position with the head elevated 30 degrees. The transducer was placed in the third or fourth intercostals space, and the measurement was made distal to the tip of the mitral leaflets for five consecutive cycles. The interventricular septum thickness, posterior wall thickness, and left ventricular internal dimensions in diastole were measured at the peak of the QRS complex on a simultaneously recorded electrocardiogram according to the Penn convention[7]. Devereux formula was divided by body surface area in square meters for measurement of left ventricular mass index (LVMI) [7]. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index (LVMI) greater than 125g/m^2 because of well documented prognostic value of this threshold in hypertensive patients[8]. After an overnight fast of 12 hours, a standardized oral glucose tolerance test (OGTT) using 75 grams of glucose was performed following WHO guidelines[9], venous sampling was done after 0, 30, 60 and 120 minutes of glucose taking. Patients with a previous diagnosis of diabetes mellitus were not submitted to the OGTT. Glucose tolerance was assessed according to American Diabetes

Association (ADA)[10] i.e. subjects with a fasting plasma glucose > 126 mg/dl and/or a 2 hour plasma glucose level > 200 mg/dl were considered to have diabetes; subjects with a fasting plasma glucose 110-125 mg/dl and with 2 hour plasma glucose level 140-199 mg/dl were considered to have impaired fasting glucose(IFG) and impaired glucose tolerance(IGT) respectively; and subjects with fasting plasma glucose < 110 mg/dl and 2 hour plasma glucose < 140 mg/dl were regarded as having normal glucose tolerance (NGT).

Serum and plasma was separated by centrifugation of blood sample and were subjected for analytical procedures. Glucose (Glucose oxidase method, CV % : 3.4)[11], cholesterol (Cholesterol oxidase method, CV % : 3.9)[12], triglycerides (Enzymatic method, CV % : 3.6)[13], HDL-C (Phosphpotungstic method, CV % : 4.7)[14], and $HbA1_C$ (Ion exchange resin method, CV % : 3.9)[15], were measured in fully automated analyzer Bayer express plus. LDL and VLDL cholesterol[16]were calculated. Plasma insulin was measured by a highly specific immunoradiometric assay (CV % : 4.1) with a two-site monoclonal antibody[17]. Microalbuminuria[18]was estimated in a random urine sample. These experiments were approved by Institutional Ethical Committee. HOMA IR was used as a surrogate for the direct measurement of insulin resistance and was calculated as follows[19]:
HOMA IR= [fasting insulin (µU/mL) ×fasting glucose (mmol/L)]/22.5.

Statistical analysis: Data analyses were performed with the SPSS 15.0 statistical software. The results for continuous variables are mean ± SD and are well within the normal curve (i.e. normality is maintained). The two tailed (unpaired) student's test for independent samples, analysis of variance (ANOVA) was used, in assessment of the significance of difference between group means. The Chi square test was used for evaluating differences in proportions between groups. For all analyses, the nominal level of statistical significance was<0.05. Pearson's correlation coefficients were obtained to estimate linear correlations between variables.

Result: Table I shows the various baseline characteristics of study population. The mean age of patients with hypertension was 50.7+ 11.4 years, and 62.7% were men. The mean reported duration of hypertension was 8.5+ 5.8 years. Elevated body weight was a concomitant health disorder for most of the patient. Ninety percent of group II patient showed a body mass index equal to or greater than 25.0 kg/m^2, and fifty percent of the patients were obese (BMI ≥30 kg/m^2). Only 6.8% of the patients were not receiving anti-hypertensive medications. Two or more antihypertensive drugs were being taken by 61% of the patients. Despite this, 71% (95% confidence interval [CI], 65.3% - 74.8%) showed uncontrolled blood pressure (≥ 140/90 mmHg). Mean (± standard deviation) fasting plasma glucose and insulin for hypertensive patients were 108.4 ± 13.8 mg/dl and 28.4± 2.6 µU/ml respectively, and the mean HOMA IR was 7.6 ± 4.2.However after excluding all the known diabetic subjects, the mean fasting glucose level was 100.8 ± 13.8 mg/dl. According to ATP III criteria[20], 64% (95% confidence interval [CI], 59% - 68%) of the patients had abnormal serum LDL-cholesterol level, and diagnosis of metabolic syndrome was made in 45.3% (95% confidence interval [CI], 41.4% - 48.9%) of the patients.

Table 1: Characteristics of study population

Characteristics	Group I (N:100)	Group II (N:325)
Age	49.3 ± 10.3	50.7 ± 11.4
Males [n (%)]	50(50%)	204 (62.7%)
BMI (kg/m^2)	22.7 ± 4.3	29.4 ± 5.7*
Waist/hip ratio	0.91 ± 0.05	0.95 ± 0.06*
Hypertension duration (years)	-	8.5 ± 6.3
Diabetes history in family (yes/no)	-	61/264
Known type 1 diabetes mellitus	-	6 (1.8%)
Known type 2 diabetes mellitus	-	40 (12.3%)
Systolic BP (mmHg)	128 ± 10	144 ± 22*
Diastolic BP (mmHg)	80 ± 8	88 ± 10*
Fasting plasma glucose (mg/dl)	84.7 ± 11.3	108.4 ± 13.8*
Mean plasma glucose during OGTT (mg/dl)	115.4 ± 21.2	148.4 ± 30.5*
HbA1c (%)	5.7 ± 0.9	7.0 ± 1.3*
Fasting insulin	14.1 ± 4.2	28.4 ± 12.6†

(µU/ml)		
Mean insulin during OGTT (µU/ml)	64.5 ± 11.7	109.5 ± 17.2†
HOMA IR	2.9 ± 2.6	7.6 ± 4.2†
LVMI (g/m^2)	-	123 ± 41
Triglycerides (mg/dl)	123.6 ± 22.8	167.7 ± 41.2*
Total cholesterol (mg/dl)	162.5 ± 29.6	201.5 ± 46.3*
HDL- cholesterol (mg/dl)	48.5 ± 6.4	43.5 ± 4.4*
LDL- cholesterol (mg/dl)	87.9 ± 20.4	123.2 ± 31.2*
VLDL- cholesterol (mg/dl)	25.4 ± 8.6	35.6 ± 9.8 *
Microalbuminuria (mg/day)	21.3± 8.2	31.4 ± 11.2*

*P<0.05 (Group II Vs Group I), †P<0.01 (Group II Vs Group I)

Plasma levels of glucose and insulin during OGTT in group I and group II are presented in table II. Results of standard OGTT and corresponding insulin response after 0, 30, 60 and 120 minutes were statistically different in two groups.

Table II: Plasma glucose (mg/dl) and insulin (µU/ml) during oral glucose tolerance test in group I and group II

Time (min)	Group I		Group II	
	Plasma glucose (mg/dl)	Plasma Insulin (µU/ml)	Plasma glucose (mg/dl)	Plasma Insulin (µU/ml)
0	84.7 ± 11.3	14.1 ± 4.2	108.4 ± 13.8*	28.4± 12.6†
30	148.6 ± 23.3	86.4 ± 20.2	161.6 ± 26.5*	98.6 ± 26.5*
60	132.4 ± 21.6	98.3 ± 22.8	174.8 ± 31.8*	141.8 ± 33.4†
90	120.7 ± 18.3	78.9 ±19.3	152.2 ± 28.1*	168.2 ± 49.9†
120	94.5 ± 13.3	46.3 ± 12.5	143.5 ± 23.7†	120.7 ± 34.2‡

*P<0.05 (Group II Vs Group I), †P<0.01 (Group II Vs Group I), ‡ P<0.001 (Group II Vs Group I)

Table III shows the prevalence of glucose abnormalities in hypertensive patients(Group II).Of the 325 patients , there were 95 (29.23%, 95% confidence interval[CI], 25.67% - 34.21%) with normal glucose metabolism.46 of the 325 patients (14.15%)reported a previous diagnosis of diabetes mellitus (6 with type 1 diabetes mellitus and 40 with type 2 diabetes mellitus). For the remaining 184 patients with no previous diagnosis of diabetes mellitus the mean fasting plasma glucose and insulin concentrations were 102.4 ± 10.1 mg/dl and 26.4± 15.3 µU/ml respectively. The mean HOMA-IR was 6.8 ± 3.1. IFG and IGT were diagnosed in 54(16.61%, 95% confidence interval[CI], 13.34% - 21.34%) and 99(30.46%, 95% confidence interval[CI], 26.83% - 33.91%) patients respectively and silent previously undiagnosed diabetes mellitus was diagnosed in 31 patients (9.53%, 95% confidence interval[CI],6.67% - 12.14%). Thus the total number of diabetic patient in this study was 77(23.69%, 95% confidence interval [CI], 20.43% - 28.25%). Mean (± standard deviation) HbA1c for diabetic patients was 8.1 ± 2.8%. However after excluding all the known diabetic subjects, the mean HbA1c level was 6.6%.The mean LVMI was 123 ± 41 g/m^2. The prevalence of LVH (defined as LVMI >125 g/m^2) was 39.38% (128 patients, 95% confidence interval[CI],35.32% - 42.44%). LVMI and severity of glucose intolerance were significantly related. LVMI was significantly higher (p<0.01) in 77 diabetic patients (133 ± 44 g/m^2) than in non diabetic patient (118 ± 34 g/m^2). Male gender, higher levels of insulin (fasting insulin/HOMA IR) and greater adiposity (BMI) were all strongly associated with the severity of glucose abnormalities. Prevalence of metabolic syndrome increased progressively with severity of glucose abnormality.

Discussion: This study shows that significant number of hypertensive patients(p<0.05, by applying SEP) have abnormal glucose tolerance which support the hypothesis that hypertension may be considered a diabetes prone condition[1]. 325 patients with essential hypertension were evaluated in this study to examine the glucose tolerance and corresponding insulin secretory response to oral glucose load. Abnormal glucose metabolism was observed in 70.77% of patients (95% confidence interval [CI], 65.87% - 74.21%). The high prevalence of glucose abnormalities was evident despite the exclusion of patients with

previously diagnosed diabetes mellitus(14.15%) that gave a prevalence of undiagnosed glucose abnormalities as high as 56.62%.(95% confidence interval[CI], 53.98% - 60.45%).

Table III: Prevalence of glucose abnormalities in hypertensive patients and associated caridometabolic risk factors profile.

	NGM	IGT	IFG	New DM	Known DM	p
n	95	99	54	31	46	
%	29.23	30.46	16.61	9.53	14.15	
Age (years)	51.3+ 7.3	48.4+ 6.8	49.5+ 8.6	50.3+ 9.9	52.8+ 9.3	< 0.05
Males [n (%)]	50 (52.63)	66 (66.66)	34 (62.96)	21 (67.74)	33 (71.73)	
BMI (kg/m2)	22.3 + 3.3	30.8 + 4.4	26.6 + 3.9	31.4 + 5.8	33.6 + 5.6	< 0.05
Fasting plasma glucose (mg/dl)	91 + 8.3	122 + 20.5	136 + 9.8	137 + 23.9	133 + 26.3	< 0.05
Fasting insulin (µU/ml)	22 + 4.7	26 + 7.6	25 + 5.9	32 + 7.3	31 + 6.8	< 0.05
HOMA IR	4.9 + 2.1	7.8 + 4.2	8.3 + 3.3	10.8 + 5.6	10.1 + 4.7	< 0.05
LVMI (g/m2)	114 + 22	126 + 27	120 + 31	130 + 35	135 + 46	< 0.05
Triglycerides (mg/dl)	132.4+ 17.2	161.8+ 28.5	156.8+ 22.6	184.1+ 26.1	192.3+ 29.3	< 0.05
Total chole. (mg/dl)	172.4+ 21.4	191.8+ 38.5	186.8+ 32.3	214.1+ 32.3	222.7+ 39.1	< 0.05
HDL- chole. (mg/dl)	46.3 + 5.3	41.8 + 6.1	40.9 + 6.9	41.4 + 5.4	39.6 + 5.1	< 0.05
LDL- chole.(mg/dl)	101 + 18.1	119 + 23.9	119 + 21.3	135 + 25.4	148 + 31.7	< 0.05
VLDL- cholesterol (mg/dl)	26 $\pm$ 7.9	34 $\pm$ 8.8	32 $\pm$ 6.3	37 $\pm$ 8.5	36 $\pm$ 7.9	< 0.05
Metabolic Syndrome (%)	7.1	23.7	30.5	48.3	59.5	< 0.05

NGM: Normal glucose metabolism; IGT; Impaired glucose tolerance; IFG: Impaired fasting glycemia; DM: Diabetes mellitus

The finding that 70.77% of essential hypertensive patients also have an abnormal glucose metabolism indicates that these two conditions may be pathophysiologically linked. It is being suggested that hypertension and type 2 DM may represent different populations with more or less overlapping pathophysiology[2] and considerable evidence indicates that the link between diabetes and essential hypertension is hyperinsulinemia[2,21].Thus, when hypertensive subjects, are compared to normotensive controls, a heightened plasma insulin response to a glucose challenge is found consistently. A state of cellular resistance to insulin action subtends the observed hyperinsulinism which is evident by the elevated mean HOMA IR in these patients. In demographically adjusted models[21], the correlation between fasting insulin and blood pressure is ≈0.1, meaning that 1% of the variance in blood pressure is attributable to insulinemia. An alternative way to express this is that a 10 µU/mL increase in the insulin concentration is associated with a 19% increase in hypertension prevalence. A number of mechanisms have been proposed to explain possible relations between hypertension and insulin resistance, including stimulation of the sympathetic nervous system[22], increases in renal sodium retention[23], modulation of cation transplant[24], and hypertrophy of vascular smooth muscle[25]. Racial differences in ion regulation have been found and could possibly account for differences in the relation between insulin and blood pressure in different ethnic groups[26]. However, acute infusion in both animals and humans in most studies have led to a vasodilatation hypotensive effect rather than a hypertensive effect[275-30]. Administration of insulin therapy to diabetic and nondiabetic participants does not lead to a hypertensive effect in the absence of hypoglycemia[31,32].

Decreasing glucose tolerance was associated with insulin resistance/hyperinsulinemia. From normal glucose tolerance condition through IGT, IFG to diabetic, the HOMA IR progressively increased (NGT: 4.9$\pm$2.1; IGT: 7.8 $\pm$ 4.2; IFG: 8.3 $\pm$ 3.3; New type 2 DM: 10.8 $\pm$ 5.6; known type 2 DM: 10.1 $\pm$ 4.7)(Table III). Hyperinsulinemia and insulin resistance may contribute to the expression of cardiovascular risk factors[33]as is evident in this study by increase in left ventricular mass index with increasing severe abnormalities of glucose metabolism. These results agree with those of De Simone et al[34] which showed a positive relationship between left ventricular mass and the presence of

an increasing number of metabolic risk factors including diabetes, obesity, and hypercholesterolemia, all of which were present in a significant number of patients in this study. In addition, the present study diagnosed impaired fasting glycemia, impaired glucose tolerance and silent undiagnosed diabetes mellitus in 56.62% of the hypertensive patients, and all of these conditions substantially increase cardiovascular risk[35], as reflected through the results of this study that all these groups have a somewhat higher levels of known cardiometabolic risk factors (BMI ≥ 25 kg/m^2, MA>30 mg/day, cholesterol ≥ 200 mg/dl, LDL-C ≥ 100 mg/dl, HDL-C ≤ 40 mg/dl, and triglyceride ≥ 150 mg/dl). This resembles the results obtained with OGTT in other high risk population admitted to coronary care units with acute myocardial infarction[36].

Nonetheless, this study has few limitations. First, that effect of antihypertensive drugs were not taken into account, and fact is that a significant number of patients with glucose intolerance were receiving diuretics, and it well known that diuretics and beta blockers negatively affect glucose metabolism. In contrast, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists and alpha receptor blockers are thought to be metabolically neutral. Second, euglycemic insulin clamp test was not used for measuring insulin resistance which is considered as a gold standard test, rather HOMA, was taken for measuring insulin resistance. Nevertheless, it had been demonstrated that there was a strong positive correlation between HOMA IR and euglycemic insulin clamp IR in type 2 diabetic subjects[37] Third, antibodies were not estimated in confirming the type 1 diabetes mellitus patients.

Conclusion: This study found different glucose abnormalities and exaggerated insulin response to glucose load (hyperinsulinemia) in essential hypertensive patients and showed that 70.77% of patients also have an abnormal glucose metabolism along with cluster of other cardiovascular risk factors, whose prevalence increases with severity of glucose intolerance. What is argued here is that, in hypertensive patients, we can do better in reducing coronary heart disease risk by routine investigations of glucose and other cardiometabolic parameter, not just their BP measurements. Although BP is most important parameter to be controlled in hypertensive patients, there are gains to be made in early detection of glucose abnormalities. Although the magnitude of added benefit from earlier detection of diabetes/abnormal glucose metabolism is uncertain, if one considers that undetected diabetes mellitus increases coronary heart diseases by a factor of 2 or more and that specific therapies are clearly effective in reducing coronary heart disease1, the magnitude of cardiac benefit from an earlier detection of diabetes may be potentially substantial. Clinical trials have demonstrated that lifestyle intervention and pharmacological therapy can reduce the incidence rate of type 2 diabetes among high-risk individuals2, and an ADA consensus statement has recommended treatment with metformin, in addition to diet and exercise, in high-risk individuals with IGT or IFG38. Physiologic maneuvers such as calorie restriction in the overweight individual and regular physical exercise can improve tissue sensitivity to insulin; good preliminary evidence shows that these measures can also lower blood pressure in both normotensive and hypertensive individuals. A strong case can therefore be made for the use of physiologic intervention in the treatment of essential hypertension to reduce the incidence of diabetes mellitus and cardiovascular disease. In summary, findings of this study have implications for the care of hypertensive patients. Patients and care providers should give the highest priority to control blood pressure and to improve glycemia control sufficiently along with other modifiable risk factors. If this can be achieved, the number of patients, in whom overt hyperglycemias develops, should decline. Substantially, this should, in turn, lower the number in whom cardiovascular disease develops.

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