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IMPACT OF LOSARTAN AND GLIBENCLAMIDE GIVEN IN COMBINATION ON THE METABOLISM IN PATIENTS WITH HYPERTENSION AND NIDDM

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Abstract:
Aim: *To observe the effect of treatment with losartan given in combination with glibenclamide on metabolism (fat and carbohydrates) and physiological factors (BMI, weight and blood pressure) in patients with hypertension with NIDDM.*
Study Design: *An Observational Study.*
Place and Duration: *In Pharmacology and Therapeutics Department in collaboration with medicine department of Mayo Hospital Lahore for three months duration from June 2018 to August 2018.*
Methods: *The collective drug therapy with tablet glibenclamide 5 mg and tablet losartan 50 mg (attuned rendering to the individual glycemic control) was given to 30 newly identified uncomplicated NIDDM patients with hypertension of both genders between thirty to fifty five years of age for a period of two months. Blood pressure and Fasting glucose were recorded one time in a week, lipid profile (VLDL, total cholesterol, triglycerides, LDL and HDL cholesterol), fasting insulin and BMI calculated during the analysis i.e. Zero and at 60 day two times.*
Results and conclusion: *Substantial reduction in fasting blood sugar (P <0.001) was observed and fasting insulin (p <0.05) was rise significantly. There were no substantial variations (P = NS) in triglycerides, VLDL, LDL cholesterol and total serum. A major rise in HDL cholesterol (P less than 0.05) was noted. Noteworthy decrease in both diastolic and systolic blood pressure (less than 0.001 P value) was observed. A negligible effect on BMI and weight. Combination treatment with glibenclamide and losartan had a major effect on fat metabolism (HDL cholesterol only), blood pressure and carbohydrate metabolism in patients of hypertension with NIDDM.*
Key Words: *Losartan, glibenclamide, physiological factors, metabolism.*

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INTRODUCTION:

Diabetes mellitus is a chronic disease that necessitates constant medical attention and training so that the patient blood sugar levels can be controlled[1-2]. In Type II diabetes has resistance of tissues to insulin and comparative decrease secretion of insulin[3]. This is a clutch of diseases categorized by hyperglycemia described by Islay et al. 1999 and related with complications like microvascular angiopathy (renal, possibly neuropathic or visual) and macrovascular (peripheral and coronary vessels)[4]. In approximately forty percent of patients with type 2 diabetes has hypertension, i.e. cardiovascular disease and diabetes have very much correlation[5]. The two independent early cardiovascular disease risk factors are diabetes and hypertension. When they happen collectively, the frequency of stroke, coronary heart disease and atherosclerosis increases numerous times. Grundy et al. 1999 said that "diabetes is a cardiac disease" The renin-angiotensin system plays a major part in hypertension and diabetic patients because it acts on the renin angiotensinogen substrate released from the juxtaglomerular apparatus of the renal system and release angiotensin I which is the byproduct of (angiotensin converting enzyme) ACE into angiotensin II[6]. Angiotensin receptors can be separated into two different AT1 and AT2 subtypes in addition to atypical AT by radioligand receptor binding studies using PD 123177 (Kang et al., 1994) and Dupe 753 (losartan)[7]. Jackson, 2001 stated that angiotensin II produced in this way has three main effects: Impaired renal function, impaired peripheral resistance and Impaired CVS structure. Losartan is the 2-N-butyl-4-chloro-5-hydroxymethyl-1-imidazole potassium salt. It is the strongest, specific after oral administration and competitive angiotensin II antagonist[8]. Removes A-II from a particular subtype of type I receptor. This A-II change provokes contraction of smooth muscle persuaded by aldosterone, arginine vasopressin release, catecholamine release, hypertrophic responses and water uptake as explained by Bauer et al in 1995)[9]. Glibenclamide is a 2nd generation oral hypoglycemic agent from the sulfonylurea group. It acts on B pancreatic beta cells, exciting secretion of insulin, and thereby decreasing glucose in plasma said by Rang et al in 2003. The ATP sensitive K + channel is its primary target explained by Gribble et al in 1998. The sulfonylureas have no effect on insulin secretion by beta cells of pancreas, but also rise peripheral tissue insulin sensitivity as by Gaines et al in 1988)[10]. This analysis planned to estimate the consequence of collective treatment with glibenclamide and losartan on carbohydrates (insulin and blood sugar) and metabolism of lipid in patients of hypertension with NIDDM.

MATERIALS AND METHODS:

This observational study was held in Pharmacology and Therapeutics Department in collaboration with medicine department of Mayo Hospital Lahore for three months duration from June 2018 to August 2018. 30 patients with newly identified, uncomplicated and untreated patients of hypertension with NIDDM were nominated from the OPD of Medicine department Unit II of Mayo Hospital Lahore. The eligibility criteria included both genders between thirty and fifty five years old, with a fasting sugar level equal to or higher than 140 mg / dL and a blood pressure ≥ 160/95 mmHg. All study participants have given consent prior to the study. Follow-up visit record, laboratory tests and preliminary data of every patient were documented in especially designed format.

The study was conducted for three months. All patients checked their diet (500 calories less than those taken) and exercise (20 to 30 minutes a day). While blood pressure and fasting blood sugar were monitored weekly, other studies such as lipid profile (total cholesterol, triglycerides, VLDL LDL and HDL cholesterol) and serum insulin levels were checked for two times during the analysis, i.e. on day zero and on day 60. Each patient was given a Losartan 50 mg solid tablet once daily. Glibenclamide was administered in 5 mg tablets (daonil) and adapted to the subject's glycemic control. Glucometer was used for fasting glucose by method of glucose oxidation. Using a sphygmomanometer, Blood pressure was monitored. Using enzyme immunoassay (MEIA) technique, serum levels of insulin were determined using the IMX insulin reagent. The lipid profile (triglycerides, HDL cholesterol and total cholesterol) was performed on spectrophotometer 21 of USA Milton Roy Company. LDL cholesterol was assessed according to formula of Friedewald's designed in 1972. VLDL = CPLASMA - CHDL - TG / 5 and Delong et al in 1990 give formula to calculate VLDL cholesterol. VLDL-cholesterol (mg / dl) = 0.20 X Triglyceride

RESULTS:

In e metabolism of carbohydrate, a significant reduction in mean fasting blood sugar was observed from 282.9 ± 23.03mg / dL on day 0 to 155.90 ± 7.90mg / dL on day 60 (Table 1). Mean insulin serum levels also exhibited substantial outcomes (p less than 0.05) rise from 7.90 ± 1.45µU / ml on day 0 to 16.92 ± 4.02µU / ml on day 60 (Table 1).

Carbohydrate Metabolism (n=30) given in Table 1

Parameters	DAY-0	DAY-60	P-VALUE
Fasting serum insulin (µU/ml)	7.90 ± 1.45	16.92 ± 4.02	< 0.05
Fasting blood glucose (mg/dl)	282.9 ± 23.03	155.90 ± 7.90	< 0.001

In metabolism of fat, insignificant increases in total cholesterol, VLDL, LDL, HDL and serum triglycerides augmented from 184.1 ± 12.01mg / dl to 210 ± 10.93 mg (P = NS). / dl, 129.01 ± 16.92 mg / dl -172.9 ± 22.96 mg / dl, 113.9 ± 5.90mg/dl to 135.01 ± 8.91 mg/dl and 26.04 ± 3.51mg/ dl to 35.04 ± 4.59 mg/dl correspondingly from day zero+ to day 60. In dissimilarity to HDL serum cholesterol exhibited a noteworthy rise (P less than 0.05) between 34.9 ± 1.10 mg / dL on day 0 and 40.01 ± 1.39 mg / dL on day 60 (Table 2).

Fat Metabolism (n=30) in Table 2

Parameters	DAY-0	DAY-60	P-VALUE
Total cholesterol	184.1 ± 12.01	210 ± 10.93	NS
VLDL-cholesterol	26.04 ± 3.51	35.04 ± 4.59	NS
LDL-cholesterol	113.9 ± 5.90	135.01 ± 8.91	NS
HDL-cholesterol	34.9 ± 1.10	40.01 ± 1.39	< 0.05
Triglycerides	129.01 ± 16.92	172.9 ± 22.96	NS

In physiological parameters, both diastolic and systolic blood pressure displayed a substantial decrease (P <0.001) between 170 ± 4.79 mm Hg to 135.01 ± 4.91mm Hg and 104 ± 2.09 mm Hg to 83 ± 2.1 mm Hg. Both patient weight and body mass index were reduced but not statistically significant (Table 3).

Changes in Weight, Mean Systolic and Diastolic Blood Pressure Level, BMI (n=30) in Table 3

Parameters	DAY-0	DAY-60	P-VALUE
Weight (Kg)	75.1 ± 4.30	71.91 ± 4.40	NS
Blood pressure (mmHg)	170 ± 4.79	135.01 ± 4.91	< 0.001
	104 ± 2.09	83 ± 2.1	< 0.001
Body mass index BMI (Kg/m2)	31.04 ± 1.90	30.05 ± 2.01	NS

DISCUSSION:

When losartan was administered with glibenclamide in combination to 30 patients of diabetes with hypertension for 2months, mean blood sugar fasting reduced from 282.9 ± 23.03mg / dL on day 0 to 155.90 ± 7.90mg / dL (p <0.001), almost% when losartan was administered alone. 44.619% (p <0.05) and 25.09% (the results of the earlier study were made by the author himself). In 1998, Paolisso et al evaluated glucose metabolism of 5.2 ± 0.4 to 6.03 ± 0.5 mg / kg x min (p <0.05) in 10 patients of hypertension after administration of 50 mg losartan for one month once daily and this is accredited to the losartan sympathetic effect, which upsurges flow of the blood, prevents glycolysis, and thus reduces clearance of glucose in patients of hypertension[11]. This analysis is consistent with our outcomes because there is a decrease in blood sugar levels. This decrease is very important, probably because of glibenclamides administration. In 1994, Tomiyama et al spontaneously tested 19 hypertensive patients with losartan for 20 weeks and stated that glucose requirements in the fixation test did not change, i.e. had no influence on blood sugar levels[12]. This is contrary to our results. Lipid profile, HDL cholesterol level in Chan et al. (1997) study noted significant results that contrast with the study, probably because the elderly were diabetic patients with albuminuria[13].

In this analysis, both diastolic and systolic blood pressure dropped significantly from 170 ± 4.79 mm Hg to 135.01 ± 4.91mm Hg and 104 ± 2.09 mm Hg to 83 ± 2.1 mm Hg, correspondingly at P < 0.001. However, weight and body mass index did not show a significant result. In 1996, MacKay et al and in 1996 Moan et al observed a substantial reduction in diastolic and systolic blood pressure[14]. In 1997, Chan et al reported a negligible decrease in BMI (kg / m2) after 3 months of treatment with losartan in 8 patients of hypertension with NIDDM, while in 1995 Laaks did not observe a significant decrease in BMI (kg / m2), but important in patients with essential hypertension[15]. Treatment with Glibenclamide- losartan has shown a valuable effect on serum insulin, blood glucose, and blood pressure and HDL cholesterol in patients of hypertension with NIDDM.

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