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EFFECTS OF ATORVASTATIN AND EZETIMIBE ON DYSLIPIDEMIA OF TYPE 2 DIABETIC PATIENTS

1. **IMRAN ALI SHEIKH**
FCPS
2. **MUZAFFAR ALI SHAIKH**
MD
3. **IKRAMUDIN UJJAN**
M.PHIL

1. *Assistant Professor*
Department of Medicine,
LIAQUAT UNIVERSITY OF MEDICAL AND HEALTH SCIENCES, JAMSHORO/ HYDERABAD, SINDH PAKISTAN
2. *Associate Professor*
Department of Medicine
LIAQUAT UNIVERSITY OF MEDICAL AND HEALTH SCIENCES, JAMSHORO/ HYDERABAD, SINDH PAKISTAN
3. *Assistant Professor*
Department of pathology
LIAQUAT UNIVERSITY OF MEDICAL AND HEALTH SCIENCES, JAMSHORO/ HYDERABAD, SINDH PAKISTAN

Correspondence to:
DR. IMRAN ALI SHAIKH
Assistant Professor
Department of Medicine
LUMHS, JAMSHORO
Email: imran5naili@hotmail.com
Cell#:03332662415

ABSTRACT

OBJECTIVE: *To observe the effects of combination of atorvastatin and ezetimibe in type 2 diabetic patients attending.*
STUDY DESIGN : *Prospective ; Observational study*
PLACE AND DURATION: *The study conducted from November 2007 to March 2008 in Medical OPDs, wards at Liaquat University of Medical & Health Sciences, Hyderabad and consulting clinics of Sadder Hyderabad.*
PATIENTS METHODS: *50 patients were selected by random sampling, out of them 30 were males and 20 were females. The age range was 35-70 years. The mean BMI was 27.*
INCLUSION CRITERIA *were type 2 diabetic patients already using atorvastatin for more than 1 month. The total cholesterol was more than 200 mg/dl, Triglycerides more than 150 mg/dl, LDL-c more than 150 mg/dl and HDL less than 35mg/dl.*
EXCLUSION CRITERIA *were type 2 diabetic patients with cardiac , advanced renal disease or nephropathy. Any history to ezetimibe, atorvastatin allergy, pregnant and lactating mothers, type 1 diabetics or any type 2 diabetic patient using immunosuppressive drugs.*
All patients were taking oral hypoglycemic agents like Glibenclamide and metformin in combination or alone for more than 2 years. No patient was on insulin. Fasting blood sugar and lipid profile were done. The LFT was done before treatment and completion of the study. Lipid profile was checked on 0, 6 and 12 weeks.
The atorvastatin was given with dose of 20 mg and ezetimibe 10 mg once a day at bed time. The data was tabulated and calculated on SPSS 15 . The p value less than 0.05 considered statically significant.
RESULTS; *After 12 weeks Total cholesterol was reduced 9% (p=<0.001), LDL-c was reduced 18%(p=<0.001) ,TG 12% (p=<0.001)and HDL increased 11%(p=<0.05)*
CONCLUSION. *Diabetes dyslipidemia is an important cause of morbidity. Patients should be keeping on combination of atorvastatin and ezetimibe. This combination is well tolerated .*

KEY WORDS: diabetes Mellitus, dyslipidemia, atorvastatin and ezetimibe.

INTRODUCTION:

The incidence of macro vascular complications are increased 2-5 folds in diabetics as compared to non diabetic patients This is attributed mainly to dyslipidemia.(1). In diabetes type 2 dyslipidemia is usually presented in the form of increased triglycerides levels ,decreased high density lipoproteins levels slightly higher low density lipoproteins as compared to non diabetics(2). Aggressive lipid lowering therapy to reduce LDL-c reduces cardiac mortality as well as total mortality.(3)

The various statins not only lower the lipid levels but also stabilize the vulnerable plaque, restore endothelial function and have anti thrombotic,anti-inflammatory and antioxidant properties.(4). The reduction of LDL-c is approximately 30-60%; a dimension never previously seen with diet or other treatment(5).

Ezetimibe represents the newest class of lipid-modifying agents. It exerts its cholesterol-lowering effect by inhibiting the absorption of both the dietary cholesterol and biliary cholesterol at the brush border of the small intestine.[6]

This inhibition leads to decreased delivery of cholesterol to the liver, resulting in increased clearance of blood cholesterol by the liver [7]

Ezetimibe appears to be most useful as part of combination therapy with other lipid-modifying agents rather than as monotherapy. Most studies have been conducted in combination with statins and have significantly reduced LDL-c by an additional 25.8% in total population compared with an additional 2.7% reduction with placebo plus statin [8]. Also, further lowering of triglyceride levels by 10% and further increase in HDL levels by 2-3% can be expected by adding ezetimibe to statins [9]

The rationale to conduct this study is to emphasize the combination of two lipid lowering agents in diabetic dyslipidemia which is more helpful to achieve the goals of NECP.

1. STUDY DESIGN:

Observational study:

MATERIAL AND METHODS:

This study was conducted at Medical OPDs, wards at Liaquat University of Medical & Health Sciences and consulting clinics of Sadder Hyderabad from Nov 2007 to February 2008.The 50 patient were selected from periphery of Hyderabad. Out of them 30 were males and 20 were females. The male to female ratio was 1.5:1 .The age ranges between 35-70 years. The mean age was 45 years . The mean BMI was 27.

The inclusion criteria were type 2 diabetic patients already using atorvastatin for more than 1 month. The total cholesterol was more than 220 mg/dl, Triglycerides more than 150 mg/dl, LDL-c more than 150 mg/dl and HDL less than 35mg/dl.(Table-1)

The exclusion criteria were type 2 diabetic patients with cardiac , advanced renal disease or nephropathy. Any history to ezetimibe, atorvastatin allergy, pregnant and lactating mothers type 1 diabetics or any type 2 diabetic patient using immunosuppressive drugs.

All were on oral hypoglycemic drugs for many years. The mean HbA1c was 8.5%. The mean fasting blood sugar was 135 mg/dl .

The lipid profile was done on 0, 6th and 12th weeks respectively in Diagnostic research laboratory of Liaquat University Hospital Hyderabad by automatic analyzer.

After inducting in the study all patient were put on combination of atorvastatin 20 mg and ezetimibe 10 mg for 12 weeks at bed time. The LFT was checked at 0 and 12th weeks.

All data was fed in SPSS version 15. The paired t test was used for comparison of lipid profiles of 0, 6 and 12 weeks .P value of less than 0.05 was considered statically significant.

TABLE NO. 1
BASE LINE CHARACTERISTICS OF 50 PATIENTS

Characters	
Number (%)	50 (M=30, F=20)
Age(mean) years	45
BMI	27
Fasting blood sugar	135
Serum cholesterol	220
LDL-c	151-200
Triglycerides	150
HDL	<35
HbA1c	8.5%

TABLE NO. 2
CHANGES IN LIPID PROFILE AT 0, 6 AND 12 TH WEEKS OF TREATMENT

Lipids	0 Week	6th Week	12th Week	P Value At 12th Week
Total Cholestrol	228	209	200	<0.001
Ldl-c	164	144	134	<0.001
Hdl	38	40	41.35	<0.05
Triglycerides	180	170	160	<0.001

RESULTS:

The 50 patients ,30 male and 20 females type 2 diabetic patients were included in this study.

The treated patients had a significant reduction in total cholesterol (-28mg/dl,-9%, p=<0.001) ,LDL-c(-30mg/dl,18% p=<0.001) .HDL cholesterol was increased (3.35 mg/dl,11% p=<0.05) but this increase was time dependant as was no significant increase observed in week 6th. While triglycerides (-20mg/dl,-12% p=<.001) were decreased at 12th week of the treatment. (Table-2)

There was no significant difference seen on base line LFT and after the completion of the study.

DISCUSSION:

Current recommendations for LDL goal of less than 100 mg/dl (an option of < 70 mg/dl in very high-risk patients), an HDL goal greater than 40 mg/dl for men and greater than 50 mg/dl for women, and a triglyceride goal less than 150 mg/dl [10.] Non pharmacologic interventions (diet and exercise) are first-line therapies and are used with pharmacologic therapy when necessary. Lowering LDL levels is the first priority in treating diabetic dyslipidemia. Statins are the first drug choice, followed by resins or ezetimibe, then fenofibrate or niacin [11]

Co administration of atorvastatin and ezetimibe is well tolerated and effective in diabetic dyslipidemia in compression to alone therapy [12] . Davidson et al shown significantly greater reductions in LDL-c and triglycerides(7.5%) and increase in HDL(2.4.%) than simvastatin alone. Co administration of simvastatin and ezetimibe is well tolerated than high dose simvastatin [13] Wendy S Madigosky et al shown statistically significant reduction in total cholesterol(-9%), triglycerides(-8%) and increase in HDL (3%).[14]

Pearson et al examined the effect of adding 10 mg of ezetimibe to the patients' current statin therapies for six weeks (40% atorvastatin, 29% simvastatin, 22% pravastatin, 10% other statins). Patients were randomly assigned 2:1 to either ongoing statin plus 10 mg ezetimibe, or ongoing statin plus placebo. The addition of ezetimibe to statin therapy further decreased LDL-c by approximately 25%. The combination of statin and ezetimibe allowed

71% of patients to reach NCEP LDL-c targets, compared with 21% on statin immunotherapy [15].In our study LDL-c reduced 18% in 12 weeks . This was because of shorter duration of the study.

Coadministration of ezetimibe plus atorvastatin was significantly (P<0.01) more effective at reducing LDL-c concentrations than atorvastatin or ezetimibe alone for both the pooled treatment groups and each atorvastatin dose. Reductions in apo B, total cholesterol, and triglycerides, as well as increases in HDL-c, were all significantly greater with combination therapy than atorvastatin alone (P<0.01) or ezetimibe alone (P0.05). Total cholesterol, HDL and LDL-c:HDL ratios also showed significant improvement with coadministration compared with atorvastatin or ezetimibe alone (P<0.01). Ezetimibe plus the starting dose of atorvastatin (10 mg) lowered direct LDL-c as effectively as the maximum dose of atorvastatin (80 mg) alone (50% and 51%, respectively), reduced median triglycerides by a similar amount (both 31%), but provided significantly greater increases in HDL (9% versus 3%)[16]. Jane-Diane Fraser recently done a study shown the percent of patients achieving their LDL-c targets on the ezetimibe/atorvastatin combination at 12 weeks was 60.5% compared with 49.7% for patients on the atorvastatin 20mg/ 40mg regimen [Odds ratio (95% CI)1.55 (1.21, 1.98)] [17].

Four phase 3 multi-centre, double-blind, randomised, placebo-controlled studies were set up to evaluate the potential of the combination of different statins (simvastatin, atorvastatin, pravastatin and lovastatin) and ezetimibe in patients with primary hypercholesterolemia. LDL-c at entry in the 12-week study was between 3.8-6.5 mmol/L and triglycerides were below 4.0 mmol/L. An average incremental LDL-c reduction of 21% (18-24%, depending on the statin used) was achieved in the combination groups compared to statin monotherapy [18].

In our study the reduction of LDL-c was 18%, triglycerides was 12% and increment in HDL was 3.35% on 20 mg of atorvastatin and 10 mg of ezetimibe.

CONCLUSION:

In our conclusion , the combination of two drugs ezetimibe and atorvastatin is more effective than single statin therapy along with anti diabetic drugs.

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