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Otiginal Article

A Comparison of Ezetimibe and Acarbose in Decreasing Liver Transaminase in Nonalcoholic Fatty Liver Disease: A Randomized Clinical Trial

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ABSTRACT

Background:
Ezetimibe inhibits the resorption of dietary and biliary cholesterol in the small intestine and decreases insulin resistance in patients with nonalcoholic fatty liver disease (NAFLD). Acarbose has been used in type 2 diabetes mellitus and metabolic syndrome. This study aims to compare the therapeutic effects of ezetimibe and acarbosein decreasing liver transaminase levels in patients with NAFLD.

Materials and Methods:
This was a single center, double-blind, parallel-group study conducted at Bu-Ali Sina Hospital, Qazvin, Iran. In this trial, we enrolled, by simple randomization, a total of 62 patients diagnosed with NASH. There were 29 patients treated with ezetimibe and 33 who were treated with acarbose over a ten-week period.

Results:
Ezetimibe treatment significantly reduced ALT, AST, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-sensitivity C-reactive protein (hsCRP), and serum insulin levels and the insulin resistance homeostasis model assessment (HOMA-IR) index compared to patients treated with acarbose (p<0.001). Ezetimibe treatment decreased ALT (p=0.05), AST (p=0.01), total cholesterol (p=0.01), HDL cholesterol (p=0.03) and LDL cholesterol (p=0.03) levels to a significantly higher extent.

Conclusion:
Both ezetimibe and acarbose improved metabolic and biochemical abnormalities in patients with NASH, however these effects were more prominent with ezetimibe.

Keywords: Nonalcoholic fatty liver disease; Nonalcoholic Steatohepatitis; NAFLD; NASH; Ezetimibe; Acarbose; Therapy

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver injury worldwide. NAFLD causes a wide spectrum of liver diseases that range from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma(1). Obesity, excess intake of calories and insulin resistance which results in an increased release of free fatty acids from adipocytes and increased rates of fatty acid synthesis in the liver are considered to be common causes of NAFLD(2,3). There are two step

in NAFLD, lipid accumulation and steatosis (first step), and necrosis, inflammation, and fibrosis (second step)(4). To date, no single therapy has been approved to treat NAFLD, however initial management must focus on lifestyle modification and the reversal of conditions associated with NAFLD.

Ezetimibe is a novel, potent cholesterol-decreasing drug that selectively binds to the cholesterol transporter Niemann-Pick C1-Like 1 (NPC1L1) and inhibits the resorption of dietary and biliary cholesterol in the small intestine and liver(5).Ezetimibe significantly decreases plasma alanine aminotransferase activity, tumor necrosis factor (TNF-α), and insulin resistance(6,7) and has a suppressive effect on fatty liver(6,8-10). In addition to these roles, recent studies suggest that ezetimibe affects insulin resistance(11). Nevertheless; the mechanism whereby ezetimibe achieves these favorable effects on insulin sensitivity are not well understood.

Acarbose, an α-glucosidase inhibitor, is another drug found to be useful in NAFLD and type 2 diabetes(12,13). A strong correlation between diabetes and NAFLD has been shown in previous studies(14,15).Acarbose improves liver function in NAFLD in patients with metabolic syndrome(16).To the best of our knowledge, no randomized clinical trial has evaluated ezetimibe and acarbosemonotherapy in humans diagnosed with NAFLD. The aim of this study was to compare the therapeutic effects of ezetimibe and acarbose in patients with NAFLD.

MATERIALS AND METHODS

From January 2011 to December 2012, we assessed 62 patients with NAFLD for eligibility to enter the study. This was a single center, double-blind, parallel-group study conducted in Bu-Ali Sina Hospital, Qazvin, Iran. Patients were randomized via simple randomization.

NAFLD was diagnosed according to the presence of widespread fat in the liver as identified by a bright liver pattern with liver-kidney contrast and vascular blurring by echotexture in ultrasonography in addition to elevations in alanine aminotransferase (ALT >40 mg/dl in men and ALT >31 mg/dl in women).

Exclusion criteria were diabetes mellitus or previous use of anti-diabetic medications that included insulin-sensitizing agents such as metformin and pioglitazone, alcohol intake exceeding 20 g/day and those who reported any signs, symptoms, and/or history of known liver disease (viral, metabolic, or autoimmune) or drug-induced liver disease, previous anti-hyperlipidemic treatment and patients with heart failure or renal failure. The study protocol was approved by the Ethical Committee of Bu-Ali Sina Hospital and informed consent was obtained from all subjects prior to enrollment in the study.

All patients were assessed by abdominal ultrasonography and biochemical tests before treatment. Neither dietary nor exercise therapy was prescribed and their lifestyles remained unchanged. Patients were randomly assigned to one of two groups according to the method of treatment: ezetimibe (n=29) and acarbose (n=33). Patients in group 1 received ezetimibe (10 mg/day) while subjects in group 2 were treated with acarbose (50 mg, twice daily). Demographic characteristics of patients in each group are shown in Table 1. All patients returned for follow up visits at our center ten weeks after beginning treatment. At the follow up visit, we obtained body weight, body mass index (BMI), serum ALT, AST, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood sugar (FBS), high-sensitivity C-reactive protein (hsCRP), and serum insulin levels and insulin resistance homeostasis model assessment (HOMA-IR) index, which were compared with baseline levels in both groups.

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, V. 16.0; SPSS Inc, Chicago, IL, USA). Data were summarized by frequencies and percentages for categorical variables and means ± SD for continuous variables. Comparison of pre- and post treatment of ezetimibe and acarbose groups were carried out using repeated measures analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Patients' ages were 40.6±2.3 years for the ezetimibe group and 40.6±10.8 years for the acarbose group (p=1). There were 16 (55.2%) patients in the ezetimibe group and 19 (61.3%) in the acarbose group who were male (p=0.8). We observed no significant differences in baseline characteristics of patients in both groups (Table 1). Ezetimibe treatment significantly reduced ALT(p<0.001), AST(p<0.001), triglycerides(p<0.001), total cholesterol(p<0.001), LDL cholesterol(p<0.001), hsCRP(p<0.001) and serum insulin levels(p<0.001). There was a reduction in the HOMA-IR index(p<0.001) as well (Table 2).

Similar results were obtained with acarbose treatment. Body weight(p<0.001), BMI(p<0.001),

Table 1: Demographic and biochemical parameters.

	Ezetimibe (n=29)	Acarbose (n=33)	*p*-value
Male (%)	16 (55.2)	19 (61.3)	0.8
Age (years)	40.6±2.3	40.6±10.8	1
Body weight (kg)	80.4±10.6	80.8 ±12.5	1
BMI (kg/m^2)	30.5±11.9	30.1±9.4	1
AST	54.7±22.5	50.8±16.6	0.3
ALT	94.6±56.0	87.5±27.8	0.4
Triglycerides	178.2±73.3	189.7±89.1	0.8
Total cholesterol	214.6±47	206.4±40.3	0.8
HDL cholesterol	42.4±7.0	39.40±8.2	0.6
LDL cholesterol	136.5±47.6	129.1±31.2	0.8
Fasting blood sugar (FBS)	98.6±12.7	94.1±14.1	0.4
Serum insulin	14.6±6.8	14.8±7.6	1
hsCRP*	2.3±2.1	2.1±2.5	1
HOMA index	3.6±1.8	3.4±1.7	0.8

*hsCRP: High-sensitivity C-reactive protein

Table 2: Patients' clinical characteristics before and after treatment.

Variables	Ezetimibe (n=29)			Acarbose (n=33)			*p*-value between ezetimibe and acarbose
	Before treatment	After 10 weeks	*p*-value	Before treatment	After 10 weeks	*p*-value	
Body weight (kg)	80.4±10.6	79.5±11.5	0.2	80.8 ±12.5	77.4±11.7	<0.001	0.04
BMI (kg/m^2)	30.5±11.9	30.1±10.9	0.2	30.1±9.4	28.8±8.5	<0.001	0.11
AST	54.7±22.5	33.2±13	<0.001	50.8±16.6	40.7±12.4	<0.001	0.01
ALT	94.6±56.0	52.8±28.4	<0.001	87.5±27.8	61.5±23.8	<0.001	0.05
Triglycerides	178.2±73.3	146.1±69.2	<0.001	189.7±89.1	161.9±68.1	<0.001	0.7
Total cholesterol	214.6±47	178.1±37.2	<0.001	206.4±40.3	189.5±32.1	<0.001	0.01
HDL cholesterol	42.4±7.0	41.0±5.7	0.2	39.40±8.2	40.6± 7.9	0.07	0.03
LDL cholesterol	136.5±47.6	107.9±35.4	<0.001	129.1±31.2	116.4±26	<0.001	0.03
Fasting blood sugar (FBS)	98.6±12.7	97.1±14.1	0.4	94.1±14.1	93.6±12.3	0.7	0.7
Serum insulin	14.6±6.8	11.12±5.7	<0.001	14.8±7.6	12.5±17.0	<0.001	0.2
hsCRP*	2.3±2.1	1.6±1.2	<0.001	2.1±2.5	1.6±1.2	0.11	0.5
HOMA index	3.6±1.8	2.7±1.7	<0.001	3.4±1.7	2.9±1.8	<0.001	0.12

*hsCRP: High-sensitivy C-reactive protein.

ALT (p<0.001), AST (p<0.001), triglycerides (p<0.001), total cholesterol (p<0.001), LDL cholesterol (p<0.001), and serum insulin levels (p<0.001), in addition to the HOMA-IR index (p<0.001) decreased significantly in this group (Table 2).

In a comparison between ezetimibe and acarbose treatment, we found that ezetimibe treatment had significantly higher decreased ALT (p=0.05), AST (p=0.01), total cholesterol (p=0.01), HDL cholesterol (p=0.03) and LDL cholesterol (p=0.03) levels. However acarbose treatment decreased body weight at a significantly higher rate compared to ezetimibe (p=0.04). No substantial differences were found in

BMI (p=0.11), FBS (p=0.7), triglycerides (p=0.7), hsCRP (p=0.5) and serum insulin (p=0.2) levels and HOMA-IR index (p=0.12) between the two groups (Table 2).

DISCUSSION

We compared the effects of ezetimibe, an intestinal cholesterol transporter inhibitor, to acarbose, an alfa-glucosidase inhibitor, as treatment for NAFLD. However, lifestyle modification and cognitive behavior therapy aimed at weight reduction with decreased calorie intake and exercise have been considered as the main therapy for this metabolic syndrome(17).

Use of insulin sensitizers, anti-oxidants, anti-obesity, herbal and lipid lowering medications can be effective(18,19).

Previous studies have researched the therapeutic effects of ezetimibe in NAFLD patients and animal models. In a study by Nazaky, ezetimibe therapy led to improvement in lipid metabolic disorders(20). Tamaki studied the effect of ezetimibe on metabolic syndrome. He observed that ezetimibe reduced serum LDL, CRP, AST, and ALT levels and increased HDL levels(21).De Bario who studied the effects of ezetimibe on NAFLD observed that inhibition of the NPC1L1 receptor and intestinal sterol influx transporter diminished serum cholesterol levels and regulated fatty acid metabolism in the fatty liver(22).

Results of a study by Fillipatose on fatty liver showed the efficacy of ezetimibe in decreasing ALT levels(23). According to Musso in a study of treatment of fatty liver, althoughezetimibe decreased plasma lipid levels and improved liver histology, it was ineffective on glucose metabolism and HbA1C levels(24). Finally, Yoshida described the efficacy of ezetimibe on dyslipidemia and decreased insulin resistance(25).

This study researched the effects of ezetimibe on the fatty liver. As with previous studies, the results noted decreased levels of ALT, AST, triglycerides, total cholesterol, LDL, FBS, serum insulin level and CRP. The Homa index which is correlated with insulin resistance improved with ezetimibe. HDL levels significantly increased with this treatment (Table 2).

Improvement of fat metabolism with ezetimibe due to inhibition of gut cholesterol absorption is expected but the additional effects on glucose metabolism and improvement in insulin resistance should be explained.

There are some studies about the effects of acarbose on metabolic syndrome. Nazaki, in his study, prescribed acarbose for efficacy on regulation of lipid profiles in metabolic syndrome, which would be synergistic with ezetimibetherapy(20). In a study by Yamagish, acarbose therapy decreased triglyceride levels and insulin resistance(26).Lieber observed decreased serum levels of a marker of inflammation(27).Letor explained that acarbose as an alpha glucosidase inhibitor decreased not only insulin resistance but also plasma cholesterol levels(28).

The results of our study about the efficacy of acarbose in fatty liver treatment showed that it decreased ALT, triglycerides, cholesterol and LDL levels. We observed increased HDL levels and improved insulin resistance. However when compared to ezetimibe, acarbose decreased plasma sugar levels more potently and was less effective in decreasing ALT and AST levels (Table 2). We observed no serious side effects from either medication during the course of the treatment.

Future research on these pathways and the use of combined therapy in treatment of NAFLD can be useful and increase knowledge about its pathophysiology.

Both ezetimibe and acarbose improved metabolic and biochemical abnormalities in patients with NAFLD. Although the decrease in body weight was significant for acarbose treatment, ezetimibe treatment decreased NAFLD abnormality to a higher extent than acarbose. Ezetimibe appeared to be a more potent agent in NAFLD treatment than acarbose. However due to differences in mechanisms of ezetimibe and acarbose, further studies of longer duration are necessary in order to clarify the efficacy of combination therapy with these two drugs.

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