Original Article

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A Comparison of the Therapeutic Effects of Metformin, Pioglitazone and Vitamin E in Patients with Non-Alcoholic Fatty Liver

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ABSTRACT

BACKGROUND AND OBJECTIVE: Non-alcoholic Fatty Liver Disease (NAFLD) is specified by changes in fat in the liver, with or without inflammation. The disease is the hepatic manifestation of metabolic syndrome. Since a different medicinal treatment has been introduced, this study was conducted to compare the therapeutic effects of metformin, pioglitazone and vitamin E in treatment of these patients.

METHODS: In this single-blind randomized clinical trial, 93 patients with the diagnosis of NAFLD who referred to Imam Reza Hospital in Kermanshah were randomly divided into three groups (n = 31). Then, the first group received two gr/day metformin, the second group received 30 mg/day pioglitazone and the third group received 800 IU/day vitamin E for 12 weeks. LFTs, BMI, HOMA-IR, FBS, and serum insulin levels were measured before and after the treatment course (IRCT: 2016010411991N3).

FINDINGS: There was no significant difference between the groups in terms of distribution of sex, mean age, LFT and HOMA-IR before treatment. The mean difference in severity of NAFLD before or after the treatment was metformin (1.06 ± 0.63), pioglitazone (1.195±0.75) and vitamin E (0.77±0.62), which was statistically significant ($p<0.05$). In addition, serum insulin levels ($p<0.01$) and HOMA-IR ($p<0.05$) were significant between the groups; pioglitazone showed highest effect on reducing the severity of NAFLD, serum insulin levels, and HOMA-IR. Metformin and vitamin E were next in line, respectively.

CONCLUSION: Based on the results of this study, pioglitazone is more effective than metformin and vitamin E both in reducing the severity of NAFLD and in lowering LFT and serum insulin levels.

KEY WORDS: *Non-Alcoholic Fatty Liver Disease, Metabolic Syndrome, Metformin, Pioglitazone, Vitamin E.*

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Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is a spectrum of liver lesions that occurs due to fat accumulation in the liver cells, leading to advanced degeneration of the liver parenchyma and leads to fibrosis and cirrhosis of the liver (1, 2). NAFLD is currently recognized as the most common cause of chronic liver disease in adults and children worldwide, and it is estimated that 14 to 30% of the American population are suffering from this disease (1-5). Its prevalence has been reported to be 32% in Iran (3). Recent studies suggest that the etiology and pathogenesis of this disease are not clear (4-7), but insulin resistance and lipid metabolism disorders seem to play a key role in increasing the amount of fat in the liver cells, and its progression towards cirrhosis has been proven (1, 7-9).

The clinical features of NAFLD are not fully understood and clinically, the affected patients are usually asymptomatic. However, elevated levels of serum aminotransferases in 90% of cases is a common symptom of the disease (2, 7-10). The main risk factors associated with this disease include obesity, high blood pressure, hyperlipidemia, cardiovascular disease, diabetes and insulin resistance. For this reason, it is recommended that NAFLD be controlled in obese and diabetic patients (7, 11,12). Due to the high prevalence, lack of information on the course of the disease and the chronic nature of the NAFLD, there are different opinions about recommending specific treatments (1,4).

Therefore, the treatment of this disease is focused on addressing underlying causes such as obesity, diabetes control and insulin resistance (1, 11,13), and many researchers have suggested a combination of appropriate diet and physical activity for the prevention and treatment of this disease (7, 14). Insulin resistance is one of the most important factors in the onset of the disease, and it can be concluded that by increasing insulin sensitivity and eliminating resistance to therapeutic treatments, desirable results can be achieved (15). In a study on obese laboratory mice, metformin has been shown to reduce fatty liver cells by reducing insulin resistance (16).

In other studies on pioglitazone, the results indicated that the drug improves the laboratory and histological parameters in patients with fatty liver by reducing insulin resistance (17, 18). In addition, since oxidative processes in the liver and its damages were found to be effective in the development of the disease, antioxidant drugs have also been considered as one of the methods for controlling the disease (7, 19, 20). Studies conducted in other countries comparing the therapeutic effect of pioglitazone, metformin and vitamin E drugs in controlling the disease concluded that the therapeutic effects of metformin and pioglitazone were better than other treatments (9, 21-23). However, no definitive treatment for this disease has been proposed so far (7, 10, 14).

This study aims to compare the therapeutic effects of metformin, pioglitazone and vitamin E on liver function tests (LFT), serum levels of insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), body mass index (BMI) and fasting blood sugar (FBS) were used to select the most effective drug.

Methods

This randomized single-blinded clinical trial was approved by the Ethics Committee of Kermanshah University of Medical Sciences with a code of P – 10 – 870 and a clinical trial number of IRTC: 2016010411991N3, and was conducted among 93 patients non-alcoholic fatty liver disease who were referred to the Endocrine Specialty Clinic of Imam Reza Hospital in Kermanshah, Iran.

Sample size was determined to be at least 22 subjects in each group using the expected effect of pioglitazone on liver enzymes (LFT) or fatty liver severity at 95% confidence level and 90% test power, and in order to increase the study power and the possibility of excluding subjects from the study during the course of treatment, the sample size was increased to 31 subjects in each group.

Patients were randomly divided into groups after obtaining informed written consent. Moreover, in this study, no additional test or cost was imposed on patients for the diagnosis and treatment. People with NAFLD (based on liver ultrasonography), aged 18 – 75 years old of both sexes, with negative viral hepatitis serology were included, while patients were excluded in case of alcohol abuse, pregnancy, diabetes, hypothyroidism, heart disease, renal failure, infectious diseases, corticosteroid use, and other manifestations of other liver diseases and history of jaundice.

At the beginning of the study, BMI and circulating serum liver enzymes including aspartate aminotransferase aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

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(ALKP), and FBS and serum insulin in the laboratory of Imam Reza Hospital were measured in all patients with NAFLD. Then, the patients were randomly divided into three groups of 31 patients.

One group received two g/day metformin, the second group was treated with pioglitazone 30 mg/day, and the third group was treated with 800 IU/day vitamin E for 12 weeks. Metformin was manufactured by Aria Pharmaceutical Company, Vitamin E was manufactured by Shahd Darou Company and pioglitazone was produced by Razi Company. At the end of the re-treatment period, the patients were evaluated and liver ultrasonography, BMI and tests were measured and recorded. In this study, BMI was calculated by dividing the weight in kilograms by squared height in meters. Insulin was also measured by the ELISA method with a Monobind kit (Monobind Inc., USA).

The insulin resistance index (HOMA-IR) was used to measure indirect insulin resistance (fasting glucose (mg/dl)×insulin (uμ / ml) divide by 405]. LFT and FBS were measured with the Pars Azmun test kits and Autoanalyser (Hitachi-902 Co.) (In this study, the cut-off point for AST and ALT was 40 IU / L for HOMA-IR and 1.64 for HOMA-IR).

To reduce the risk of measurement error, all patients were evaluated by a sonographer and by GE-x200 ultrasound before and after the treatment. Furthermore, for the steady and consistent diagnosis of fatty liver, liver echogenicity ratio was given to the radiologist as follows:

- Zero or normal status
- Grade 1 or mild: Increased parenchymal echogenicity with a fine structure of the liver (echogenicity similar to the renal cortex).
- Grade 2 or Medium: Exacerbation of ultrasound beam reduction and weakening of certain parts of the liver (visible portal vein).
- Grade 3 or severe: Reduced visibility of portal and hepatic vein due to compression by parenchyma with surrounding fat, as well as further reduction of ultrasound beam (unobservable portal vein) (24).

After entering data into SPSS16 software, for comparison of quantitative variables with normal distribution, paired t-test, one-way ANOVA and LSD post-test (least significant differences) were used, for comparison of quantitative variables with abnormal distribution, Kruskal-Wallis test, The Mann-Whitney post hoc test were used, and for comparison of groups before and after treatment Wilcoxon test was used, and $p<0.05$ was considered significant.

Results

In this study, 93 patients with NAFLD were studied in three medicinal groups, while 36 (38.7%) were male and 57 (61.3%) were female. The mean age of the patients was 43.87±10 years. Mean BMI before treatment in the metformin group was 31.9±1.98, in the pioglitazone group was 30±1.45 and in the vitamin E group was 28.7±2.12.

There were no significant differences between the groups in terms of sex, age, BMI, AST, ALT, ALKp, insulin levels, and HOMA-IR before the treatment. After the treatment, the variables of NAFLD severity, BMI, AST, ALT, HOMA-IR and serum insulin levels were statistically significant before treatment and after treatment in all three groups. FBS variable was only significant in metformin and pioglitazone groups ($p<0.05$) (table 1).

To compare the effect of drugs on the studied variables, the differences in variables were analyzed for each variable among drug groups before and after treatment. The mean differences before treatment were significant for the variables of NAFLD severity, serum insulin level and HOMA-IR between the groups ($p<0.05$).

Regarding the decrease in NAFLD severity, insulin and HOMA-IR levels, pioglitazone was most effective and metformin and vitamin E were next in line, respectively. Regarding the BMI, however, although these differences were not significant according to the one-way ANOVA analysis, the metformin group showed a higher reduction compared to vitamin E group, in comparing mean values using LSD method (least significant differences) ($p = 0.042$). Moreover, regarding the reduction in the variables of AST and ALT, pioglitazone showed the highest effect among the three drug groups.

There was no significant difference in the reduction of FBS based on the results of analyzing the variance between drug groups in general. In addition, there was a significant difference in the level of serum insulin and HOMA-IR levels ($p<0.05$). The subsequent scheduled comparisons showed that there was a significant difference between pioglitazone and vitamin E ($p=0.007$) (table 2).

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Table 1. Comparing the mean of studied variables before and after treatment in all three groups

Variable \ Drug groups	Metformin Mean±SD		Pioglitazone Mean±SD		Vitamin E Mean±SD	
	Before	After	Before	After	Before	After
Severity of fatty liver disease (based on liver echogenicity)	1.87±0.12	0.81±0.22 (p<0.001)	1.71±0.64	0.52±0.8 (p<0.001)	1.39±0.48	0.61±0.53 (p<0.001)
BMI	31.9±1.98	31.2±1.25 (p<0.001)	30±1.45	29.5±1.44 (p=0.007)	28.7±2.12	28.4±1.96 (p=0.018)
AST	33.3±11.18	27.2±13.96 (p=0.020)	36.9±16.33	27±12.86 (p=0.014)	30.3±12.19	24.6±15.44 (p=0.002)
ALT	42.6±14.28	29.5±11.56 (p=0.002)	49.3±12.27	33.8±13.11 (p=0.018)	37.4±16.58	28.5±13.85 (p=0.002)
ALKp	183.5±38.75	175.4±29.97 (p=0.195)	218.7±34.19	196±33.46 (p=0.075)	187.5±25.98	178.3±29.76 (p=0.172)
FBS	100.7±8.11	92.5±9.47 (p=0.014)	97.6±10.21	87.5±9.34 (p=0.005)	90.8±12.22	88.6±11.68 (p=0.283)
Serum insulin levels	11.72±4.98	9.5±5.25 (p<0.001)	11.2±3.18	7.9±2.26 (p<0.001)	8.6±2.98	7±3.33 (p<0.001)
HOMA-IR	2.87±1.12	2.2±0.98 (p<0.001)	2.9±1.95	1.7±1.34 (p<0.001)	1.96±2.08	1.58±1.82 (p<0.001)

Table 2. Comparison of mean differences before and after treatment for the studied variables in the three groups of drugs

Variable \ Drug groups	Metformin Mean±SD	Pioglitazone Mean±SD	Vitamin E Mean±SD	P-value
Severity of fatty liver disease (based on liver echogenicity)	1.06±0.63	1.19±0.75	0.77±0.62	0.04
BMI	0.71±0.85	0.51±0.98	0.27±0.62	0.123
AST	6.1±13.88	9.9±21.11	5.7±9.34	0.510
ALT	13.1±21.7	15.5±34.4	8.9±14.9	0.582
ALKp	8±33.7	22.5±67.8	9.3±36.9	0.436
FBS	8.1±17.4	10±18.5	2.2±11.3	0.143
Serum insulin levels	2.2±1.49	3.3±2.55	1.5±0.92	0.009
HOMA-IR	0.67±0.63	1.2±1.46	0.38±0.33	0.027

Discussion

In this study, all three drugs of metformin, pioglitazone and vitamin E had considerable and significant effects on the studied variables, especially the NAFLD severity, AST, ALT, serum insulin levels, and HOMA-IR, indicating the therapeutic effect of each of these drugs in the treatment of NAFLD. However, pioglitazone was more effective than the other two drugs. The results of this study is consistent with studies by Shadid et al. (25), Al-Gharabally et al. (26), Belfort et al. (27), Sanyal et al. (28), Aithal et al. (29) on pioglitazone, Nair et al. (30), Marchesini et al. (31), Nobili V (32) about metformin, Harrison et al. (33), and Aghah et al. (34) about vitamin E. Based on the studies done so far, few studies have been done to compare the therapeutic effect of these drugs (21). Therefore, making such comparisons is very important for choosing the best and most effective drug. In this study, the effect of two drugs, metformin and pioglitazone, on the reduction of NAFLD severity was higher than that of vitamin E, while pioglitazone showed a lower reduction than metformin, although the difference was not significant. Razavizade et al. aimed to compare the therapeutic effects of pioglitazone and metformin at intervals of two months and four months, on 80 patients with NAFLD, and found that after two months of treatment, the levels of liver enzymes in the pioglitazone group significantly improved, while it did not change in the metformin

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group. However, after four months of treatment, metformin and pioglitazone both decreased the level of liver enzymes, cholesterol and HOMA-IR, but there was no statistically significant difference between the therapeutic effects of these two drugs, although the decrease in liver enzymes in the pioglitazone group was more than the metformin group (21).

Boettcher et al. (23), Sanyal et al. (35), and Tiikkainen et al. (36) also achieved similar results in their studies. Therefore, it seems that pioglitazone is more effective in controlling and reducing the severity of fatty liver. As expected from previous studies (9, 21, 22 and 37), in this study, metformin significantly reduced weight and BMI more than two other drugs, and there was a significant difference between the two groups of metformin and vitamin E. In this case, vitamin E showed the least effect.

Therefore, it seems that the administration of metformin in patients with high weight may be considered as a better alternative than vitamin E. Regarding the reduction of liver enzymes (AST and ALT), although the difference between drug groups was not significant in this study, the mean reduction in both variables in the pioglitazone group was more than the other two, which was consistent with the studies by Razavizade et al. (21), Ahmed et al. (7) and Vernon et al. (38). It seems that insulin-sensitizing drugs can improve the biochemical presentation and the content of fatty liver in patients with NAFLD. In some studies, it has been shown that thiazolidines reduce fat in the liver (39), which is consistent with the effect of pioglitazone on reducing NAFLD severity. Regarding the decrease in the FBS variable, pioglitazone and metformin showed a lower reduction than vitamin E. In addition, regarding the decrease in variables of serum insulin levels and HOMA-IR, pioglitazone was more than two other drugs. This indicates higher effectiveness of pioglitazone in reducing insulin resistance, and demonstrates the potential of this drug. Promrat et al. (18) also reported similar results regarding the effect of pioglitazone on insulin resistance.

In general, although no approved drug has yet been specified by the Food and Drug Administration (FDA) for the treatment of NAFLD but given the potential pathogenesis for this disease (insulin resistance, oxidative stress), drugs that increase insulin sensitivity (such as metformin and pioglitazone) and drugs that reduce oxidative stress (such as vitamin E) are used to treat this disease. Moreover, according to the results of this study, it was found that pioglitazone is more effective than the other two in treating the disease, but it requires more controlled randomized studies before it is selected as the main NAFLD treatment.

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