The effect of pioglitazone and metformin on non-alcoholic fatty liver: A double blind clinical trial study

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Abstract

Introduction: Non-alcoholic fatty liver is one of the most prevalent digestive diseases in the world and its prevalence is increasing rapidly. The objective of this study was to compare the treatment effect of pioglitazone and metformin on fatty liver.
Materials and methods: This double blinded clinical trial study was performed in 2012 among patients referring to gastrointestinal clinics in the city of Ilam. 105 non-alcoholic fatty liver patients were selected and participated in this study. Patients were randomly divided into two groups of metformin and pioglitazone. Using double blinded clinical trial, one group was treated by pioglitazone (30 mg daily) and the other by metformin (500 mg daily) both for 3 months. Then using sonography, the severity of fatty liver was compared in the two groups.
Results: Multivariable logistic regression showed that there was no significant difference between the effect of pioglitazone and metformin on the treatment of fatty liver ($p=0.92$). There was a significant difference between severity of fatty liver and BMI before treatment ($p<0.004$) but it was not confirmed after the treatment. There was also a significant difference between the severity of fatty liver and gender before treatment ($p<0.003$) but it was not confirmed after treatment. There was a negative significant relationship between age and the treatment effect of metformin but not in the pioglitazone group.
Conclusions: Both pioglitazone and metformin had a notable effect on the treatment of fatty liver solely while there was no significant difference between their effectiveness. The effectiveness of metformin was higher among males compared to that of pioglitazone.

Keywords: Fatty liver, NAFLD, pioglitazone, metformin,

Introduction

Non-alcoholic fatty liver (NAFLD) is one of the most prevalent digestive diseases in the world, particularly among obese people, and its prevalence is increasing rapidly. Its prevalence ranged from 25-70% among different countries (1-3). NAFLD can proceed to a non-alcoholic hepatitis and finally result in cirrhosis or even hepatocellular carcinoma. The prevalence of cirrhosis in NAFLD has been reported up to 25% (4-7). Prevention and control of fatty liver is important at the primary stages. Different studies have reported that metformin can cause insulin sensitivity by reduction of gluconeogenesis and intervention in the

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consumption and reabsorption of glucose; however, pioglitazone causes a distribution of the fat from muscle and liver to the fat tissue and therefore affects the sensitivity of insulin in liver and skeletal muscles (8). There is an insulin resistance among patients with NAFLD and metformin and pioglitazone are two different classes of drugs that affect insulin sensitivity. They also have a considerable effect on the disease; therefore, the current study was triggered to compare the effectiveness of the two above-mentioned drugs among patients with confirmed fatty liver in the city of Ilam.

Materials and methods

Among patients referring to gastrointestinal clinics in the city of Ilam, 105 patients diagnosed with confirmed NAFLD were selected and participated in this study. They were randomly divided into two groups of pioglitazone (53 participants) and metformin (52 participants). Excluding criteria were: patients with alcohol consumption, Cushing syndrome, Cirrhosis, patients with renal failure, heart failure, and those with intolerability of metformin or pioglitazone. Using double blind clinical trial, one group was treated by pioglitazone (30 mg daily) and another group by metformin (500mg daily) both for 3 months. At first, sonography was applied for each patient at the start of study. After 3 months, the severity of fatty liver (mild, moderate, severe) was evaluated by comparison of new and primary sonography. Finally, the results of metformin and pioglitazone groups were compared for any significant differences.

Results

Among 105 participants, 57.1% were males aging 15 to 50 years old. 46 patients (44%) were in age group of 36-45 yrs and 4 patients (4%), were in age group of 15-25 years. The weight of participants ranged from 60-80 kg from whom 56 patients (53%) were over 70kg. 56% of patients had a normal BMI (18.5-24.5), 40% were overweight (BMI= 25-29.5) and 3% were obese (BMI>30).

Three patients (2.9%) had concurrent diseases such as diabetes or cholesterolemia and 2.9% of participants had a medication history such as oral contraceptive while others (97.1%) had no medication history .

According to the biopsy and sonography reports, most patients had a mild to moderate fatty liver and only 17.1% had a severe fatty liver. The results of control sonography (after treatment) showed that 94.3% of patients had a mild to moderate fatty liver and only 5.7% had severe fatty liver which indicated a positive effect of metformin and pioglitazone on fatty liver disease.

There was not a significant difference between age and the severity of fatty liver before or after the treatment ($p>0.05$). There was a significant difference between the severity of fatty liver and BMI before treatment ($p<0.004$), but it was not confirmed after the treatment ($p=0.64$). There was a positive relationship between BMI and moderate to severe fatty liver. There was also a significant difference between the severity of fatty liver and gender before the treatment ($p<0.003$) but it was not confirmed after the treatment ($p=0.18$). The moderate and severe fatty liver was more frequent among males and the mild fatty liver was equally prevalent in both genders (Table1).

Before treatment with metformin, 15 patients (28.9%) had mild fatty liver, 30 patients (57.7%) moderate fatty liver and 7 patients (13.5%) severe fatty liver; however, these figures changed to 36 (69.2%) mild, 14 (26.9%) moderate and 2 (3.9%) severe fatty liver, respectively indicating the considerable effect of metformin on the fatty liver.

Before treatment with pioglitazone, 9 patients (17%) had mild, 33 patients (62.3%) moderate and 11 patients (20.8%) severe fatty liver; however, these figures

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changed to 28 (54.7%.) mild, 20 (37.7%) moderate and 4 (7.6%) severe fatty liver, respectively indicating the positive effect of pioglitazone on the fatty liver (Tables 2-4).

Table 1. Distribution of patients with fatty liver based on their gender and type of medication.

Severity of fatty liver		Drug of used	Total				Gender		P
			Male		Female		N	%	
			N	%	N	%			
Before treatment	Mild	Metformin	62.5	15	45.8	11	16.7	4	P=0.003 *df*=1 X^2=8.7
		Pioglitazone	37.5	9	4.2	1	33.3	8	
		Total	100	24	50	12	50	12	
	Moderate	Metformin	47.6	30	20.6	13	27	17	
		Pioglitazone	52.4	33	22.2	14	30.2	19	
		Total	100	63	42.9	27	57.1	36	
	Severe	Metformin	38.9	7	22.2	4	16.7	3	
		Pioglitazone	61.1	11	1.1	2	50	9	
		Total	100	18	33.3	6	66.7	12	
After treatment	Mild	Metformin	55.4	36	26.2	17	29.2	19	P=0.18 *df*=1 X^2=1.8
		Pioglitazone	44.6	29	13.8	9	30.8	20	
		Total	100	65	40	26	60	39	
	Moderate	Metformin	41.2	14	29.4	10	11.8	4	
		Pioglitazone	58.8	20	23.5	8	35.3	12	
		Total	100	34	52.9	18	47.1	16	
	Severe	Metformin	33.3	2	16.7	1	16.7	1	
		Pioglitazone	66.7	2	0	0	66.7	4	
		Total	100	6	16.7	1	83.3	5	

Table 2. Comparison between the severity of fatty liver before and after treatment with metformin and pioglitazone.

Severity of fatty liver before treatment				Severity of fatty liver after treatment						Total	
				Mild		Moderate		Severe			
		N	%	N	%	N	%	N	%	N	%
Metformin	Mild	15	62.5	15	28.8	0	0	0	0	15	28.8
	Moderate	30	47.6	19	36.5	11	21.2	0	0	30	57.7
	Severe	7	38.9	2	3.8	3	5.8	2	3.8	7	13.5
	Total	52	100	36	69.2	14	26.9	2	3.8	52	100
pioglitazone	Mild	9	37.5	9	17	0	0	0	0	9	17
	Moderate	33	52.4	18	34	15	28.3	0	0	33	62.3
	Severe	11	61.1	2	3.8	5	9.4	4	7.5	11	20.8
	Total	53	100	29	54.7	20	37.7	4	7.5	53	100

After disregarding of some confounding variables such as age, gender and BMI, the results of multivariable logistic regression showed that there was no significant difference between the effect of pioglitazone and metformin on the treatment of fatty liver (Table 4).

There was a significant relationship between gender and the type of treatment ($p<0.02$). The group of metformin included 46.2% males and the group of pioglitazone included 67.9% males.

Regarding BMI, there was no significant difference between 2 groups of treatment; however, the mean age of participants in the metformin group was 3.5 years higher than those in the pioglitazone group. There was a negative significant relationship between age and the rate of improvement in the metformin group, but not in the pioglitazone group (Table 4).

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Table 3. The frequency of betterment rate among patients with fatty liver based ontheir medication.

Type of medication	Betterment rate						Total	
	Completely treated		Relatively treated		Untreated			
	N	%	N	%	N	%	N	%
Metformin	2	3.8	22	42.3	28	53.8	52	100
pioglitazone	2	3.8	23	43.4	28	52.8	53	100
Total	4	3.8	45	42.9	56	53.3	105	100

Table 4. The relationship between the effect of age and BMI on the betterment of fatty liver based on the treatments.

Treatment	Variable	B coefficient	Standard deviation	Wald	df	OR		P
						Lower limit	Upper limit	
Metformin	Age	0.077	0.037	4.35	1	0.862	0.995	0.037
	BMI	-0.087	0.143	0.373	1	0.693	1.21	0.54
	Constant rate	5.17	3.84	1.80	1	-	-	0.17
Pioglitazone	Age	0.044	0.041	1.16	1	0.965	1.13	0.28
	BMI	0.22	0.15	2.01	1	0.918	1.70	0.15
	Constant rate	-7.33	3.84	3.63	1	-	-	0.057

Both McNamara and binomial tests showed that either metformin or pioglitazone had a significant effect on the treatment of fatty liver alone ($p<0.0001$).

Discussion

Metformin is attributed to biguanide drugs cluster and pioglitazone is attributed to thiazolidinedione drugs cluster. These 2 medications are used widely for diabetic diseases. The conception of using these drugs for NAFLD was triggered during the past decade.

The current study investigated 105 patients with fatty liver attending ~~to~~ gastroenterology clinics in the city of Ilam and their fatty liver was confirmed as mild, moderate and severe on the basis of sonography reports. The other methods for diagnosis of fatty liver are biopsy, CT scan, and MRI. Sonography is a preferred method since other methods of diagnosis are invasive or expensive and may be accompanied by some side effects.

Both metformin and pioglitazone had a significant effect on the treatment of fatty liver lonely and there was no significant difference between the effectiveness of these drugs in the treatment of fatty liver.

No similar study had been carried out in Iran to investigate the effects of metformin or pioglitazone on fatty liver. However, some international studies have compared the effect of metformin or pioglitazone and placebo in a limited way for this purpose. Most studies have reported the effectiveness of both metformin and pioglitazone on fatty liver in comparison to placebo (9). In the current study, both McNamara and Binomial tests showed that either metformin or pioglitazone had a significant effect on the treatment of fatty liver alone.

Belfort et al studied the effect of pioglitazone accompanied with low fat regiment among patients with fatty liver and compared them with placebo and finally reported a significant improvement in the treatment group compared with placebo (9). The result of that study was consistent with what was obtained in the current study.

Another study by Nair et al. reported that applying metformin, accompanied with a usual nutritional regiment, among patients with fatty liver for 12 months caused a reduction in hepatic enzymes and hepatocellular inflammation (10). The result of that study was in line with our

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study. Some more studies have applied metformin or pioglitazone among patients suffering from fatty liver with some minor methodological variations such as limitations of lipid intake, using vitamin E, duration of the project study and all of them supported the positive effects of these drugs on improving fatty liver (11-21). The current study was the first research to compare the effects of these 2 drugs among fatty liver patients which revealed that both drugs were suitable for this purpose. However, metformin was more effective than pioglitazone in the treatment of fatty liver among males.

Conclusion

There was a negatively significant relationship between age and improvement speed in the metformin group but not in the pioglitazone group. Both metformin and pioglitazone had a significant effect on the treatment of fatty liver alone and there was no significant difference between the effectiveness of these drugs in the treatment of fatty liver. Also, metformin was more effective than pioglitazone in the treatment of fatty liver among males.

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