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

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

referring Among patients 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) metformin and (52)participants). Excluding criteria were: patients with alcohol consumption, Cushing syndrome, Cirrhosis, patients with renal failure, heart failure, and those intolerability of metformin pioglitazone. Using double blind clinical trial. one group was treated bv 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 (mild, moderate, severe) 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

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				To	otal	Gender			
		Drug of	Male		Female				P
		used					N	%	1
			N	%	N	%			
		Metformin	62.5	15	45.8	11	16.7	4	
	Mild	Pioglitazone	37.5	9	4.2	1	33.3	8	P=0.003 df=1 X^2 =8.7
		Total	100	24	50	12	50	12	
Before	Moderate	Metformin	47.6	30	20.6	13	27	17	
treatment		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	
	M(1.1	Metformin	55.4	36	26.2	17	29.2	19	
	Mild	Pioglitazone	44.6	29	13.8	9	30.8	20	
		Total	100	65	40	26	60	39	D 0 10
After treatment	Moderate	Metformin	41.2	14	29.4	10	11.8	4	P=0.18
		Pioglitazone	58.8	20	23.5	8	35.3	12	df=1 $X^2=1.8$
		Total	100	34	52.9	18	47.1	16	$\Lambda = 1.8$
	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				S	everity o	Total					
				Mild		Moderate		Severe		Total	
N %				N	%	N	%	N	%	N	%
	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
Metformin	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
	Mild	9	37.5	9	17	0	0	0	0	9	17
pioglitazone	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).

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

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

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

Treatment		B coefficient	Standard deviation			OR		P
	Variable			Wald	df	Lower limit	Upper limit	•
	Age	0.077	0.037	4.35	1	0.862	0.995	0.037
Metformin	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 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

study. Some more studies have applied metformin or pioglitazone among patients suffering from fatty liver with some minor methodological variations 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-The current study was the first 21). 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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References

- 1. Bedogni G, Miglioli L, Masutti F, Castiglione A, Croce LS, Tiribelli C, et al. Incidence and natural course of fatty liver in the general population: the Dionysus study. Hepatology. 2007; 46(5):1387-91.
- 2. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40(6):1387-95.

- 3. Farrell GC, Larter CZ. Non-alcoholic fatty liver disease: from steatosis to cirrhosis Hepatology. 2006; 43(2 Suppl 1):S99-S112.
- 4. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. The importance of metabolic factors for the increasing prevalence of fatty liver in Shanghai factory workers. J Gastroenterol Hepatol. 2007; 22(5):663-8.
- 5. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med. 2005; 143(10):722-8.
- 6. Kunde SS, Lazenby AJ, Clements RH, Abrams GA. Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women. Hepatology. 2005; 42(3):650-6.
- Papatheodoridis GV, Goulis J, Christodoulou D, Manolakopoulos S, Raptopoulou M, Andrioti E, et al. High prevalence of elevated liver enzymes in blood donors: associations with male gender and central adiposity. Eur J Gastroenterol Hepatol. 2007; 19(4):281-7.
- 8. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, et al. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol. 2006; 21(1 Pt 1):138-43.
- 9. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006; 355(22): 2297-307.
- 10. Nair S, Diehl AM, Wiseman M, Farr GH, Jr., Perrillo RP. Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. Aliment Pharmacol Ther. 2004; 20(1):23-8.
- 11. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, et al.

- Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2004; 19(5):537-44.
- 12. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005; 100(5):1082-90.
- 13. Nobili V, Manco M, Ciampalini P, Alisi A, Devito R, Bugianesi E, et al. Metformin use in children with nonalcoholic fatty liver disease: an open-label, 24-month, observational pilot study. Clin Ther. 2008; 30(6):1168-76.
- 14. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterol. 2008; 135(4):1176-84.
- Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet. 2001; 358(9285):893-4.
- 16. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a

- treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2005; 21(7):871-9.
- 17. Carulli L, Lonardo A, Lombardini S, Marchesini G, Loria P. Gender, fatty liver and GGT. Hepatology. 2006; 44(1):278-9.
- 18. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology. 2004; 39(1):188-96.
- 19. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006; 355(22):2297-307.
- 20. Chalasani NP, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, et al. Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design. Contemp Clin Trials. 2009; 30(1):88-96.
- 21. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005; 100(5):1082-90.