Effects of Orlistat or Telmisartan on the Serum Free Fatty Acids in Non-alcoholic Fatty Liver Disease Patients: An Open-Labeled Randomized Controlled Study

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Abstract

Background: *One of the important inducers of inflammatory responses and accumulation of fat in hepatocytes is free fatty acids which ultimately lead to the development of non-alcoholic fatty liver disease. Patients with non-alcoholic fatty liver disease have high levels of plasma free fatty acids which are usually associated with type 2 diabetes and components of metabolic syndrome including dyslipidemia. Objective of this research is to investigate the effects of orlistat (a lipase enzyme inhibitor) or telmisartan (an angiotensin receptor blocker) on the serum free fatty acids in non-alcoholic fatty liver disease patients taking into consideration the baseline lipid profile.*

Methods: *This open-label clinical trial was carried out in the Department of Pharmacology, College of Medicine at the University of Sulaimani in cooperation with Shar Teaching Hospital in Sulaimani city-Kurdistan Region of Iraq. A total number of 74 non-alcoholic fatty liver disease patients were recruited and grouped randomly into group I (n = 25) treated with orlistat (120 mg/day orally) for 12 weeks, group II (n = 24) treated with telmisartan (20 mg/day orally) for 8 weeks, and group III (n = 25) treated with placebo (carboxymethyl cellulose) once daily. Fasting serum level of free fatty acid and lipid profile including total cholesterol, triglyceride, high-density lipoprotein, and non-high-density lipoproteins were determined.*

Results: *Orlistat and telmisartan significantly reduced the triglyceride-glucose index and free fatty acid levels ($P < .001$) in patients with non-alcoholic fatty liver diseases.*

Conclusion: *Short-term treatment with orlistat or telmisartan produce effective and significant reductions in FFAs in patients with non-alcoholic fatty liver disease compared to placebo. Orlistat effectively reduces the free fatty acid irrespective of the baseline lipid profile.*

Keywords: *Free fatty acids, lipid profile, non-alcoholic fatty liver disease, orlistat, telmisartan*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is considered to be a very common chronic hepatic disorder recognized by the presence of hepatic steatosis and/or a large amount of lipid deposited in hepatocytes in the absence of excessive alcohol consumption.[1] It is commonly associated with type 2 diabetes (T2D), obesity, and metabolic syndrome.[2] Additionally, it is characterized by an increased level of plasma free fatty acids (FFAs) and dyslipidemia due to increased hepatic fatty acid synthesis, decrease fatty acid catabolism,[3] oxidative stress on hepatocytes[4] inflammatory/immune responses, and endoplasmic reticulum stress.[5] Plasma levels of FFA, total cholesterol, lipoproteins, and triglyceride (TGs) are elevated in patients with NAFLD.[6,7] It is well known that the main circulating fatty acids in the plasma are palmitic, palmitoleic, stearate, oleic, and linoleic acids[8] but previous studies demonstrated that one single fatty acid type can influence dyslipidemia.[9]

Usually in hepatocytes of NAFLD patients, the largest portion of lipids is stored as a triglyceride.[10] Several other lipid metabolites such as FFA, diacylglycerol, free cholesterol (FC), cholesterol ester (CE), ceramide, and phospholipids can also accumulate,[11,12] but hepatic lipid loading seems to be mainly determined by the FFA availability in the circulation.[6] The most important other potential mechanisms involved in hepatocyte fat accumulation are the overwhelmed mitochondrial oxidation of FFA, glucose inducing de-novo lipogenesis, and defect

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in the export of TG in the form of very-low-density lipoproteins (VLDL).[6,13]

Previous studies demonstrated that the circulating apoptotic cell death level at a cutoff value of 395 U/L indicates non-alcoholic steatohepatitis and is significantly correlated with the metabolic indices.[14] Serum fatty acids levels are significantly higher in a non-alcoholic steatohepatitis than the corresponding control levels and significantly correlated with the circulating apoptotic cell death.[15] Moreover, hepatocyte apoptosis played an important pathological role in the NAFLD.[16] Therefore, higher serum FFA could be served as a biomarker of liver cell apoptosis and hepatic fibrosis.

Orlistat is a weight-reducing drug that inhibits the activity of the gastric and pancreatic lipase, improves dyslipidemia, and reduces plasma levels of non-esterified fatty acids.[17,18]

Telmisartan, an angiotensin receptor blocker, has been shown to have no beneficial effect on dyslipidemia but can reduce the plasma levels of FFAs through its effect on peroxisome-proliferator activated receptor-γ (PPAR-γ) and insulin sensitization.[19] The rationale of this study is that both orlistat and telmisartan may have an effect on the circulating level of FFAs independent on the individual's lipid profile. This open-label controlled randomized pilot study aimed to compare the effect of orlistat or telmisartan on the circulating FFAs taking into consideration the baseline levels of lipid profile.

MATERIALS AND METHODS

The University's Ethical and Scientific Committee reviewed the interventions, investigations, and duration of treatment of each intervention and approved the study according to their own guidelines. In addition, they stated that the patients are free to refuse participation or continuation of intervention at any time they wanted. Finally, patients who accepted to participate in this study signed a consent form.

Setting

The present study was performed in the Department of Pharmacology, College of Medicine at the University of Sulaimani in collaboration with Shar Teaching Hospital in Sulaimania city/Kurdistan Region of Iraq through the period of August 2017 to June 2018.

Design

Eligible patients were of both sexes and not less than 18 years old. The criteria of inclusion were patients who had high serum liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes with positive findings of hepatic fatty infiltration on ultrasonography. Patients with other liver diseases (viral hepatitis, autoimmune hepatitis, etc.), HIV infection, alcoholics, drug addicts, pregnant women, and lactated nursing, and patients treated with drugs that act on the liver were excluded according to the laboratory tests carried out in the hospital. A total number of 74 patients (29 males and 45 females), whose ages ranged from 27 to 68 years old fulfilled the above criteria. The patients were grouped randomly (using randomized tables) into:

- Group I (n = 25): NAFLD patients treated with 120 mg/day of orlistat tablet for 12 weeks. Orlistat (Onlefit®) was generously provided byHikma Pharmaceutical Company, Jordan.
- Group II (n = 24): NAFLD patients treated with 20 mg/day of telmisartan tablet for 8 weeks. Telmisartan (Micardis®) was generously provided by Bohringer Pharmaceutical Company, Germany.
- Group III (n = 25): NAFLD patients treated with capsules containing carboxymethyl cellulose once daily, served as a placebo-treated group. Carboxymethyl cellulose was generously provided by Pioneer Pharmaceutical Company in Sulaimani city, Kurdistan region of Iraq.

Consultants of gastroenterology and liver diseases examined each patient clinically, and then the following measurements were determined:

Anthropometric Measurements

The anthropometric measurements for the study participants included body weight (kg) by sensitive electronic balance, height (m), and waist circumference (cm). Then body mass index (BMI) and conicity index were calculated using the following formula;

$$\text{BMI (kg/m}^2\text{)} = \text{body weight (kg)}/[\text{height (m)}]^2$$

$$\text{Conicity index} = \text{waist (m)}/[0.109 \times \sqrt{\text{weight (kg)}/\text{height (m)}}]$$

Laboratory Investigations

After 12 hours of overnight fasting, 5 mL of venous blood was drawn from each patient both before and after completing the treatment and collected into test tubes without anticoagulants and centrifuged at 3000 rpm for

15 minutes for separation of the serum and determination of liver enzymes (ALT and AST), fasting serum glucose and lipid profile (including total cholesterol, triglyceride, and high-density lipoprotein-cholesterol), and FFAs using Cobas-311 autoanalyzer and ELISA technique according to the instruction of their manufacturers.

Non-high density lipoprotein-cholesterol (NHDL-c) and triglyceride-glucose index (TYGI) were calculated by using the following equations:

Fasting serum NHDL-c = fasting serum total cholesterol (mg/dL) – fasting serum high density lipoprotein cholesterol (mg/dL),

Triglyceride-glucose index = ln (logarithm) of fasting serum glucose (mg/dL) × fasting serum triglyceride (mg/dL).[20]

Statistical Analysis

The results are expressed as number, percentage, and mean ± standard deviation. The difference between the means of the two groups was analyzed using the two-tailed independent two-sample *t*-test. Paired *t*-test was used to analyze the effectiveness of treatment in each group. One-way ANCOVA and Levene's test were also used to determine the effect of baseline lipid profile on the post-treatment fatty acid level. $P \leq .05$ is the cutoff level of significance. Excel software (2010) and the Statistical Package for Social Sciences version 24.0 software (IBM Corp.; Armonk, NY, USA) were used for data analyses.

Table 1. Baseline Characteristic Data of the Study Participants

Variables	Results (n = 74)
Gender (male : female)	29 : 45
Age (years)	43.3 ± 9.0
Residency (rural : urban)	8:66
Current smoking (%)	8 (10.8)
Current medical illnesses	
Diabetes mellitus (%)	17 (23)
Thyroid disorders (%)	14 (18.9)
Anthropometric measurements	
Waist circumference (cm)	107.3 ± 9.6
Body mass index (kg/m^2)	33.8 ± 5.6
Conicity index	1.329 ± 0.069
Liver enzymes	
Alanine transaminase (IU/L)	42.5 ± 21.6
Aspartate transaminase (IU/L)	28.4 ± 13.5
Fasting serum glucose and lipid profile (mg/dL)	
Glucose	118.6 ± 31.9
Total cholesterol	185.9 ± 31.9
Triglyceride	168.7 ± 84.4
High-density lipoprotein	40.3 ± 9.6
Non-high density lipoprotein	145.6 ± 30.1
Triglyceride-glucose index	8.151 ± 1.56
Free fatty acids (mg/dL)	35.4 ± 10.6

The results are expressed as number (%) and mean ± standard deviation.

RESULTS

Table 1 shows the baseline data of patients at the time of entry into the study. The ratio of females to males is 1.55 : 1, and the mean age of patients is 43.3 years. Most of the cases (98.2%) were residents in the rural area and only 10.8% were current smokers. Diabetes mellitus and thyroid dysfunction diseases were concomitantly associated with NAFLD by 23% and 18.9%, respectively. Anthropometric measurement values indicated that the patients were obese. Laboratory investigations showed that 43 out of 74 patients had a high level of ALT that exceeded the upper cutoff normal value of 40 IU/L. The mean level of triglyceride exceeds the upper normal value of 150 mg/dL.

Group I (orlistat-treated) patients showed significant ($P < .001$) changes in TYGI and FFAs while each serum triglyceride, total cholesterol, HDL-c, and NHDL-c were non-significantly changed compared to pre-treatment values (Table 2). Group II (telmisartan-treated) patients reported the same results as group I (orlistat-treated) patients, that is, significant ($P < .001$) reduction in both TYGI and FFA but non-significant reduction in each serum triglyceride, total cholesterol, HDL, and non-HDL values (Table 2). While group III (placebo-treated) patients, in contrast to the other 2 drug-treated groups showed significant changes in serum total cholesterol ($P = .003$) and NHDL-c ($P = .001$) measurements (Table 2).

Levene's test showed the inequality of error variance and there were significant differences in the percentage of FFA decrease for each lipid profile (Table 3). Table 4 shows the effectiveness of orlistat in reducing the fasting FFAs by using a one-way ANCOVA test while controlling for each lipid profile and TYGI. The post hoc Bonferroni test showed that there was a significant difference between orlistat and placebo ($P < .001$) and orlistat and telmisartan ($P = .010$-$.013$) (Table 4).

Table 2. Effects of Different Therapeutic Regimens on the Fasting Serum Lipid Profile

	Group III (n = 25)			Group I (n = 25)			Group II (n = 24)		
Metabolic Determinants	Before	After	*P*	Before	After	*P*	Before	After	*P*
Triglyceride (mg/dL)	173.6 ± 90.2	153.5 ± 80.1	.076	165.4 ± 71.1	155.0 ± 71.4	.490	167.2 ± 93.8	162.9 ± 75.3	.782
Total cholesterol (mg/dL)	185.4 ± 31.8	172.9 ± 31.5	.003	182.8 ± 36.2	171.3 ± 32.5	.140	189.3 ± 27.6	180.5 ± 30.0	.110
High density lipoprotein (mg/dL)	42.4 ± 11.3	43.2 ± 10.2	.534	39.6 ± 6.6	42.4 ± 17.2	.441	38.6 ± 10.3	37.9 ± 10.9	.656
Non-high density lipoprotein (mg/dL)	143.0 ± 27.7	129.7 ± 31.5	.001	143.2 ± 36.0	128.9 ± 32.6	.105	150.7 ± 26.1	142.6 ± 30.3	.142
Triglyceride-glucose index	9.094 ± 0.673	8.958 ± 0.628	.141	6.159 ± 0.786	4.821 ± 0.275	<.001	9.244 ± 0.208	4.845 ± 0.218	<.001
Free fatty acids (mg/dL)									
Fasting serum glucose (mg/dL)	32.9 ± 6.3	34.4 ± 9.2	.334	36.3 ± 11.2	29.5 ± 9.5	<.001	37.0 ± 13.1	35.4 ± 12.6	<.001
Systolic blood pressure (mm Hg)	120.9 ± 36.4	118.1 ± 39.3	.263	124.6 ± 39.8	110.4 ± 26.1	.103	107.5 ± 14.3	112.9 ± 19.4	.481
Diastolic blood pressure (mm Hg)	134.4±20.0	131.3±19.5	.203	133.5±20.5	134.7±19.0	.763	147.8±12.1	132.3±20.4	<.001
Waist circumference (mm Hg)	83.9 ± 13.3	80.5 ± 11.3	.073	84.8 ± 11.3	82.5 ± 11.3	.364	92.3 ± 7.0	86.9 ± 9.4	.002
Body mass index (kg/m^2)	107.7 ± 12.7	106.8 ± 13.2	.349	109.1 ± 7.6	106.4 ± 7.2	.001	104.7 ± 7.3	103.7 ± 7.6	.09
Free fatty acids (mg/dL)	33.9 ± 7.4	33.9 ± 7.2	.447	35.4 ± 4.8	34.7 ± 4.7	.002	31.8 ± 3.3	31.7 ± 3.4	.275

The results were expressed as mean ± standard deviation. *P* value was calculated by using a two-tailed paired Student's *t* test. Group I, orlistat-treated; group II, telmisartan-treated; and group III, placebo-treated.

Table 3. Levene's Test of Equality of Error Variance and Tests Between Subjects

	Levene's Test of Equality of Error Variance		Tests of Between-Subjects			
Controlling Lipid Profile	*F*	*P*	*F*	*P*	Partial, η^2	%
Triglyceride	8.010	.001	13.115	<.001	0.273	27.3
Total cholesterol	7.896	.001	13.077	<.001	0.272	27.2
High-density lipoprotein	7.582	.001	13.352	<.001	0.276	27.6
Non-high-density lipoprotein	7.890	.001	13.207	<.001	0.27.4	27.4
Triglyceride-glucose index	7.869	.001	13.346	<.001	0.273	27.3

Table 4. Estimated Margin Means of Fasting Serum-Free Fatty Acids Changes and Pairwise Comparison in Percentage of Free Fatty Acids

Treated Group	Triglyceride (168.7)	Total Cholesterol (185.8)	High-Density Lipoprotein (40.3)	Non-high Density Lipoprotein (145.5)	Triglyceride-Glucose Index
Placebo	105.05 ± 3.164	105.08 ± 3.158	105.29 ± 3.185	105.17 ± 3.157	105.06 ± 3.140
Orlistat	82.28 ± 3.163	82.35 ± 3.163	82.21 ± 3.159	82.37 ± 3.156	82.27 ± 3.140
Telmisartan	95.98 ± 3.28	95.88 ± 3.229	95.81 ± 3.237	95.77 ± 3.234	95.98 ± 3.205
Placebo versus orlistat (*P*-value)	<.001	<.001	<.001	<.001	<.001
Placebo versus telmisartan (*P*-value)	.146	.137	.125	.125	.140
Orlistat versus telmisartan (*P*-value)	.010	.012	.011	.013	.110

Analysis of covariance test was used for adjusting each variable of lipid profile.

DISCUSSION

The results of this study showed that short-term use of orlistat or telmisartan reduces FFAs and TYGI significantly regardless of the baseline lipid profile in patients with non-alcoholic fatty liver diseases.

Orlistat, a gastrointestinal lipase inhibitor, has been shown to reduce dietary fat absorption and is used effectively as a therapeutic option in the management of obesity.[21] Several studies have shown that orlistat has a tendency to reduce the levels of serum triglycerides, remnant-like particles, cholesterol, and FFAs[22,23] indicating beneficial effects in NAFLD patients occasionally by the same mechanism involved in weight reduction. In our study, orlistat produced a non-significant effect against the fasting serum triglyceride. This may be due to the short duration of treatment with a once-daily dose of orlistat and a small sample size of patients in our study compared to the others. Another study[24] demonstrated that orlistat can improve obesity and fat accumulation in the body of NAFLD patients but produces a non-significant effect on lipid profile, which is similar to our findings.

Telmisartan, the angiotensin II receptor antagonist has been shown to affect the distribution of fat throughout the body and reduce visceral fat content[25] but it did not improve the lipid profile including serum triglyceride, total cholesterol, HDL-c, and NHDL-c. This may explain the recommendations made by previous studies for using a lipid-lowering agent with telmisartan in NAFLD patients to produce a maximum beneficial effect on the metabolic derangement produced by the disease process.[26] As we mentioned earlier, in addition to the blood pressure-lowering effect, telmisartan activates the PPAR-γ receptor in hepatocytes.[19] This activation may in part explain the effectiveness of telmisartan in NAFLD patients by promoting pleiotropic cleavage of Fndc5 (fibronectin type III domain-containing protein 5) gene product and an increase in the level of myokine hormone known as irisin[27] that enhances the browning of subcutaneous white adipose tissue. It is also known that the brown adipose tissue or brown fat shows high mitochondrial content and uncoupling protein 1 (UCP1) expression leading to increased energy expenditure and heat production.[28,29] As a result, it is not unusual for our study to report that short term treatment with low doses of telmisartan produces a non-significant alteration in lipid profile in NAFLD patients, while the significant reductions in the triglyceride-glucose index and FFA level reported in this study may add another index for explaining the beneficial role of telmisartan in improving insulin resistance in NAFLD patients.

On the other hand, the placebo-treated NAFLD patients reported significant reduction and improvement in some parameters like total cholesterol and NHDL-c values. This unexpected improvement may be explained by lifestyle modifications and dietary changes made by some of these patients when they knew the diagnosis of their condition. This finding is observed in neither orlistat nor telmisartan-treated patients.

We conclude that short-term therapy with orlistat or telmisartan reduce significantly the serum levels of FFA and body fat content in NAFLD patients through different mechanisms. Orlistat is superior to placebo or telmisartan therapy in reducing the serum fatty acids irrespective of the baseline levels of serum lipid indicating the specificity of orlistat against FFAs in non-alcoholic fatty liver disease.

Ethics Committee Approval: Ethical committee approval was received from the ethical committee of Sulaimani University Faculty of Medicine (no: 54, August 15, 2017).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: Consept – M.S.M.A.; Design – M.S.M.A.; Supervision – M.O.M.; Data Collection and/or Processing – V.A.W.E., M.S.M.A.; Analysis and/or Interpretation – V.A.W.E., M.S.M.A.; Writing Manuscript – V.A.W.E.; Critical Review – V.A.W.E., M.S.M.A., M.O.M.

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Declaration of Interests: The authors declare that they have no competing interest.

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