Non-Alcoholic Fatty Liver Disease Responce to Orlistat Therapy in Iraqi Type 2 Diabetic Obese Patients

Faris Abdul Kareem Khazal

ABSTRACT:

BACKGROUND:

Non alcoholic fatty liver disease is now recognised as the most common liver disease. insulin ressistance, Increase serum free fatty acids and oxidants incorporate in the pathogenesis leading to a syndrome extended from Simple mild steatosis to steatohepatitis to cirrhosis.

OBJECTIVE:

The aim to evaluate the effect of orlistat on features of fatty liver disaese in addition to glucose and lipid profile.

METHODS:

This is A prospective study of 60 type2 diabetic obese patients had evidence of non alcoholic fatty liver disease on ultrasound examination followed for 4 months with orlistat therapy, and asses BMI, waist circumfrence, glucose control, liver function, lipid profile and ultrasound features before and after 4 months.

RESULTS:

Orlistat therapy decrease BMI, liver size, echogenisity by U/S, and triglyceride level significantly and increase

HDL also significantly,but also decrease FPG, 2hPG, HbA1c, serum cholesterol,ALT and waist circumference with insignificant statistical value, while had no effect on prothrombin time and total serum protein.

CONCLUSION:

Orlistat therapy is beneficial adjuvant therapy in obese type 2 diabetics , it reduce BMI, and U/S manifestations

of NAFLD, it also correct dyslipidemia and possibly had positive effect on glucose control and liver enzymes.

KEY WORDS:Non alcoholic fatly liver disease ,orlistat ,iraqi ,diabetics.

INTRODUCTION :

given the increasing rates of obesity, nonalcoholic fatty liver disease (NAFLD) the hepatic consequence of obesity has become the most common cause of chronic liver disease.[1]

Information on the prevelance of NAFLD depends on the diagnostic criteria used and the population studied and usually varies from 5-29% which is close to metabolic syndrome prevelance of 22%[2].The actual prevalence of NAFLD in type 2 diabetes and obesity is unknown. It is estimated that 75% of type 2 diabetic patients present some form of nonalcoholic fatty liver of different degrees. An association of NAFLD with hyperinsulinemia, as well as with clinical features of insulin resistance, has frequently been reported [3]. As far as obesity is regarded, steatosis has been reported in 70% of obese and 35% of lean patients and NAFLD in 18.5% of obese and 2.7% of lean patients. In a consecutive study[4]NAFLD represents a spectrum of hepatic disorders characterized by macrovesicular steatosis, with histology ranging from "simple" steatosis to nonalcoholic steatohepatitis (NASH). The latter represents a shift from fatty infiltration to an inflammatory/fibrosing disease that may progress to cirrhosis.[5,6]

Insulin resistance is a universal phenomenon in patients with NAFLD. the prevalence of the metabolic syndrome with type 2 diabetes mellitus

Alkindy College of Medicine, University of Baghdad, Consultant Physician, Alkindy Teaching Hospital

and NAFLD was 74% compared with 41% in those without NAFLD. The odds of having NAFLD were 3-fold greater among patients with diabetes and the metabolic syndrome compared with patients with diabetes without the metabolic syndrome. A clue to the presence of the metabolic syndrome, and perhaps NAFLD, is the regional fat distribution: Predominant central (visceral) obesity is a more reliable marker of insulin resistance than is the amount of total body fat. Waist circumference and waist-hip ratio correlate with visceral fat, and a waist circumference > 80 cm for females and >102cmformale is believed to be related to the metabolic syndrome.[7,8]

Increased levels of free fatty acids in serum lead to increased fatty acid delivery to the liver, which triggers steatohepatitis by adversely affecting hepatocytes and interfering with insulin function and mitochondrial beta-oxidation. Insulin resistance precedes the accumulation of fat in hepatocytes, and excessive intracellular fatty acid accumulation triggers oxidative stress, which in turn, generates cytokine release.[9]ultrasound is useful noninvasive way of examination and it is optimal if fatty changes involve more than 33% of liver cells.The main aim of treatment is to prevent cirrhosis and its complications, the modes of therapy available for the time being are; life style modification therapy (includind diet,weight reduction and excersize), bariatric surgery, insulin sensetising agents(metformin, glitazones), lipid lowering agents(fibrates,statins), antioxidants ,anticytokines and antiobesity(orlistat,subutramin).[11]

Orlistat, a reversible inhibitor of gastric and pancreatic lipases, blocks the absorption of approximately 30% of dietary triglycerides and was approved by for the management of obesity. Data indicate that 38% of patients treated with orlistat and a low-fat diet for 1 year lose at least 5-10% of their baseline bodyweight.[12]

METHODS:

This prospective non-controlled clinical trial was conducted for the period from June 2006 till March 2007, 60 obese type 2 diabetes mellitus patients randomly selected incorporated in this prospective study with mean age of 48.5 years, and SD of _+6.5 and mean BMI 34.8 kg/m2 and SD _+3.8, all had ultrasound evidence of NAFLD including hepatomegally, increase echogenisity and vascular blurring. all patients had no history of alcohol ingestion or drugs causing fatty infiltration as steroid, estrogem , tamoxifin, methotroxate, amiodarone and diltiazim. the pateints are HBsAg, HCV, and ANA negative and there were no stigmata of chronic liver disease.

all patients BMI were taken and tested for fasting and 2 hours prandial glucose(2hPG), HbA1c, fasting triglycerides, cholestrol and HDL, liver function including ALT.PT and total serum protein, in addition to ultrasound examination before and 16 weeks after orlistat 120mg tds with meals .

The data collected were introduce to accouter prepare spss vession 11 t.test was used to find the differences between the groups Pvalue less than the a.s controlled co be significant .

RESULTS:

Table (1) shows that 60 patients were included in this study 40 females and 20 males, all of type 2 diabetes, middle age group and insignificant mean age between the two groups, and although both groups had significant obesity but there was no significant difference in the mean body mass index(BMI) between the two groups. all our patients from the same culture and had the same diet habits and traditions.

Table (2) shows that the mean fasting blood glucose(FBG) before orlistat therapy was moderately elevated and although it declines after orlistat therapy but the decline was insignificant, same results also found on testing the 2 hours prandial glucose(2hPG) and glycated hemoglobin(HbA1c) were the decline was also insignificant.

Table (3) compare body mass index(BMI) before and after theray and there was significant decline but inspite of that mean waist size show insignificant decline

In Table (4) some of the liver function tests was coorelated to orlistat therapy, inspite of mild elevation of ALT before the therapy its decline after therapy is of no significance, prothrombin time(PT) and total serum protein were normal before and after therapy with insignificant change.

Some of the lipid profile estimation was shown on Table (5), there was significantly high level of total triglycerides before therapy which declines significantly after therapy, also high density

lipoprotein(HDL) level which was low before therapy significantly elevated after therapy, while the decline in total cholesterol was insignificant.
Ultrasound findings of the liver in Table (6) show significant improvement after orlistat therapy for both liver size, echogenesity, and perivascular blurring.

Table – 1:Patients according to gender

	No.	Age	BMI
Female	40	Means± SD 48.2 ± 5.3	Means± SD 35.3 ± 3.1
Male	20	49.1 ± 6.5	34.1 ± 3.8
Total	60	48.5 ± 6.5	34.8 ± 3.8
P Value > 0.05			

Table – 2:Glucose control before and after orlistat therapy in mg/dl

	FBG	2hPPG	HbA1C
Before	140 ± 34	201 ± 23	8.1 ± 0.5
After	132 ± 26	193 ± 36	7.9 ± 0.6
P Value	0.2 Non significant	0.39 Non significant	0.51 Non significant

T able – 3:Bmi in kg/m² and waist circumference in cm before and after orlistat therapy

	BMI	Waist
Before	34.8 ± 3.8	109 ± 5
After	31.1 ± 2.9	105 ± 3
P Value	0.019	0.074
	Significant P < 0.05	Non significant P > 0.05

Table – 4:Liver function test before and after orlistat therapy

	ALT	PT	T. S.Alb
Before	43 ± 21	14.25 ± 1.1	5.2 ± 1.2
After	29 ± 11	14.1 ± 0.95	5.1 ± 0.5
P Value	0.0741 Non significant	0.926 Non significant	0.875 Non significant

Table – 5:Lipid profile in mg/dl before and after orlistat therapy

	T.TG	T.Chl	HDL
Before	246 ± 52	195 ± 22	38 ± 6
After	213 ± 45	191 ± 36	45 ± 8
P Value	0.010 Highly significant	0.59 Non significant	0.026 Significant

Table -6:Ultrasound findings before and after orlistat therapy

	Liver Size	Increase Echogenesity	Perivascular Blurring
Before	16.5 ± 2.6	60 100%	60 100%
After	14.8± 1.9	33 55%	42 70%
P Value	0.05 (≈Significant)	0.0004 Highly significant	0.001 Highly significant

DISCUSSION:

Although NAFLD was Unrecognised complication of diabetes, obesity and hypertriglyceridemia[13] it is also common, as 66% of patients with type2 diabetes and BMI over 30 and 90% of those with BMI over 39 had this complication[14], we still do not know the size of this problem in iraqi diabeteic patients but apperantly it is also common.

Many types of therapy was suggested for this problem including life style modification, statin, insulin sensitizers, antioxidants, hepatoprotective agents, and fibrates but still weight loss is the cornerstone of therapy and so diet, excersize, bariatric surgery, and antiobesity drugs including subutramin and orlistat are another choices[15]. Patients who are not responding to excersize and diet are incorporated in this study.

Although this study is randomised noncontroled study, the sample contain more women than men while there was no significant difference in mean age and body mass index between them this is also seen by Qari in saudia arabia[16].

Orlistat therapy had significant effect on mean BMI where about 10% weight loss occur, this is also noticed by Harrison[12] and Kelly[17] where the recommended loss of weight is 0.5-1 kg/week to prevent worsening of NAFLD[18]. Waist circumference decreament was not significant statistically may be because some of our patients had generalize rather than visceral obesity.

Decrease in mean FPG, 2hPG, and HbA1c after orlistat therpy had been noticed by this study but it was not significant statistically, but other studies like Miles *et al*[19] had significant difference, this difference possibly because of the dieting habits and flactuation of diet regeimn and more carbohydrate consuming.

Some of the liver function tests was performed in this study, where the mean total serum protein and prothrombin time are normal before and after orlistat Means± SD therapy which my rise only in sever cases. But possibly because of the mild elevation of mean alanine transferase (ALT) level, the decrease in the mean level after orlistat therapy was not significant statistically ,while Harrison[12] show significant decrease in the level of ALT and that is also possible because of the longer period of therapy(6 months).

Effect of orlistat therapy on lipid profile in this study show significant decrease in mean total triglyceride level and significant increase in mean of high density lipoprotein level and insignificant decrease in mean level of total cholesterol, while Hatzitadios[20] show decrease in both triglyceride and cholesterol level.

The degree of echogenisity on ultrasound examination reflects the degree of steatosis and not the degree of fibrosis[21], this study show significant decrease in echogenisity, liver size and perivascular blurring after therapy and that is also seen by Franzese[22].

CONCLUSION:

Orlistat therapy had significantly affected the ultrasonic findings of nonalcoholic fatty liver disease by decreasing the liver size, echogenisity and perivascular blurring, it also decrease the triglyceride level and increase high density lipoprotein level and decrease the body mass index as well. It possibly also cause better control of glucose and decrease liver enzyme leve.

REFERENCES:

1. Max Bayard *et. al.* Non alcoholic fatty liver disease;American Family Medicine June 1 2006;73 .
2. Ford ES, Giles WH, Dietz WH. prevelance of metabolic syndrome among US adults. *JAMA* 2002;287:356-9.
3. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P, Rizzetto M: Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. *Hepatology* 2002;35:367–372,.
4. Wanless IR, Lentz J: Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990;12:1106–1110.
5. Duseja A, Sialy R, Das A, *et al*. Insulin tolerance test is comparable to homeostasis model of assessment for insulin resistance in patients with NAFLD. Gastroenterology. 2006;130:A-821.
6. Toshikuni N, Nakashima A, Omoto M, *et al*. NAFLD in Japanese patients with type 2 diabetes: clinical features and risk factors Gastroenterology. 2006;130:A-594.
7. Sundaram V, Northup G, Nadkarmi M, *et al*. Metabolic syndrome is a major risk factor for NAFLD among patients with non-insulin dependent diabetes mellitus. Gastroenterology. 2006;130:A-824.
8. Sobhonslidsuk A, Jongjirasiri S, Wisedopas N, *et al*. Waist Circumference as a determinant of visceral fat in NASH. Gastroenterology. 2006;130:A-820.
9. Howard BV. Insulin resistance and lipid metabolism. *Am J Cardiol* 1999;84:28J-32J.
10. Falck-YtterY *et. al.*,clinical features and nature history of non alcoholic statosis syndrome. semin liv dis 2001;21:81-8.
11. NC McAvoy, A Lockman, PC Hayes;Non alcoholic fatty liver disease:an overview.jour RCP(ed) 2007;37,9-16.
12. S.A. Harrison; C. Fincke; D. Helinski; S. Torgerson; P. Hayashi A Pilot Study of Orlistat Treatment in Obese, Non-Alcoholic Steatohepatitis Patients,aliment Pharmacol Ther 2004;20:623-628,.
13. Sanyal A J *et al*, AGA, technical review on NAFLD, gastroeneterology 2002;123; 1705-25.
14. Angulo P, Non alcoholic fatty liver disease NEJ med;346;1221-31.
15. NC MicAvoy, A Lockman, PC Hayes; NAFLD an overview the jornal of the royal college of edinburgh march 2007 ;37, issue 1;9-16.
16. Qari FA, Al-chamdi A, fatty liver in overweight and obese patients in western part of saudia;a study of sonological prevelance; *Pak.J.Med*.2005 ;(2)143-7.
17. David E Kelly *et al;* clinical efficacy of orlistat therapy in overweight and obese patients with insulin treated type 2 diabetics.Diabetes Care 2002;25;1033-41.
18. Sanyal AJ. Technical review on NAFLD. Gastroenterology 2002; 123; 1705-25.
19. John M Miles, Lawrence Leiter, *et al.* effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. Diabetes Care 2002;25; 1123-28.
20. Hatzitdios A,Savopoulos C,*et al*. Efficacy of omega-3 fatty acids,atorvostatin and orlistat in NAFLD with dyslipidemia. Indian Gastroenterology 2004;23; 131-4.
21. Matheisen UL,Franzen LE,Aselius H,Resjo M,*et al.* increase liver echogenisity at ultrasound examination reflects degree of steatosis. Dig Liv Dis 2002,34;516-22.
22. Franzese A,Vajro P,Argenziano A,Puzziello A,*et al.* Liver involvment in obese children; ultrasound and liver enzymes level at diagnosis and during follow up in italian population. Dig Dis Sci 1997;42;1428-32.