Comparison of Effect of Pentoxifylline and Lifestyle Modification on Histological Activity of Nonalcoholic Steatohepatitis Patients: A One Year Randomised Control Trial

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Abstract

Objective: Nonalcoholic steatohepatitis (NASH) can progress to cirrhosis of liver as well as hepatocellular carcinoma. Both pentoxifylline and lifestyle modification may affect nonalcoholic fatty liver disease activity score (NAS). In this study our main goal was to compare effect of pentoxifylline and lifestyle modification on NAS.

Method: This randomized control trial (RCT) – a prospective interventional study was carried out at Bangabandhu Sheikh Mujib Medical University from January 2013 to December 2015. Twenty seven Patients with biopsy proven NASH were randomized in two groups**:** PL group and L group. PL group (n= 18) received pentoxifylline 400 mg three times daily along with lifestyle modification and L group (n=9) received only lifestyle modification for one year. After one year liver biopsy was repeated. Index and end of study NAFLD activity score and fibrosis score was compared between PL & L groups by a single pathologist to avoid inter observer variation.

Result: The overall mean NAFLD activity score (NAS) improvement in PL group was 2.44±1.62 and in L group was 0.89 ± 1.05. The difference of NAS improvement between two groups were statistically significant (P = 0.01). On the other hand, mean Fibrosis score improvement in PL group was -0.17 ± 0.98 and in L group was 0.00 ± 0.71. The difference of Fibrosis score improvement between two groups were not statistically significant (P= 0.66). NAS ≥ 2 or Fibrosis score ≥1 improvement was considered as significant histological improvement (Histological responder). Per protocol analysis revealed that NAFLD activity score (NAS) ≥2 improvement occurred in 14 patients out of 18 patients (77.78%) in PL group and in 2 patients out of 9 patients (22.22%) in L group. The difference in term of responder between PL and L group was statistically significant (P= 0.004).

Conclusion: Pentoxifylline was safe, well tolerated and improved overall histology of NASH patients significantly.

[Shaheed Syed Nazrul Islam Med Col J 2021, Jan; 6 (1):112-121]

Keywords: Nonalcoholic steatohepatitis, Pentoxifylline, NAFLD activity score, Fibrosis score.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is now one of the most common liver diseases worldwide. NAFLD is a condition pathologically linked to metabolic syndrome by the intervention of Insulin resistance (IR) , characterized by hepatic steatosis in absence of significant alcohol use, hepatotoxic medications or other known liver disease.[1] The prevalence of NAFLD is 20 % - 30 % and for NASH it is 3.5 % - 5%. [2] NAFLD occurs in patients of both genders, all ethnicities and in all age groups including children. NAFLD is a broad term consisting of patients with simple steatosis (Non-alcoholic fatty liver), Non-alcoholic steatohepatitis (NASH), Non-alcoholoicsteatohepatitisrelated cirrhosis and Non-alcoholic steatohepatitis related hepatocellular carcinoma (HCC).

Simple steatosis is defined as presence of fat in the liver with or without the presence of lobular inflammation on histology.

Non-alcoholic steatohepatitis (NASH) is defined as steatosis and inflammation associated with the presence of one of the three additional features: ballooning of hepatocytes, Mallory hyaline and fibrosis on liver histology.

NASH probably causes around 80% of cases of cryptogenic cirrhosis and progresses to advanced fibrosis in 32 % -37 % of patients.[3] Obesity, Type 2 DM with insulin resistance (IR) increases the risk of fibrosis progression. Thus between 5% - 20% of non cirrhotic NASH patients develop cirrhosis during a 10 year follow up[4] and perhaps 1 in 200 NASH patients will develop hepatocellular carcinoma (HCC) over a 7 year follow up.[5]

The pathogenesis of NASH is multifactorial, inflammatory activation clearly plays a pivotal role in the disease progression. Chronic inflammation interplaying with increased oxidative stress, cytokine production, direct lipotoxicity and autoimmunity is implicated in NAFLD pathophysiology by increasing NASH, fibrosis and insulin resistance.[6] Patients with NASH have significantly higher levels of serum TNF-$\alpha$and IL-6 than seen in patients with simple steatosis.[7] Furthermore, the expression of cytokines is higher in those patients with more severe NASH. Among the proinflammatory molecules, TNF-α has been proposed to be the key link between obesity and insulin resistance.[8] Cytokines including TNF-α, a proinflammatory cytokine and adiponectin, an anti-inflammatory cytokine are believed to play an important role in hepatocellular damage, inflammation and fibrogensis in NASH. [9]

Currently NASH is managed by lifestyle modification as well as standard therapeutic intervention to control concomitant disease eg. Type 2 DM, hypertension and dyslipidemia.

Pentoxifylline (PTX) is a phosphodiesterase inhibitor. Phosphodiesterase the hydrolysis of cAMP to adenosine monophosphate (5AMP). Inhibitor of this enzyme leads to elevated level of cAMP. Elevated level of intracellular cAMP inhibit cytokine production through inhibition of activation of monocytes & lymphocytes. PTX has anti-inflammatory properties and it is known to specifically suppress TNF- α gene transcription & preventing synthesis.[10] PTX is known to decrease oxidative stress[11] and also have hydroxyl and peroxyl radical scavenging effects[12]and specifically inhibits lipid peroxidation.[13] Thereby PTX plays an important role in inhibition of second hit hypothesis required for pathogenesis of NASH.

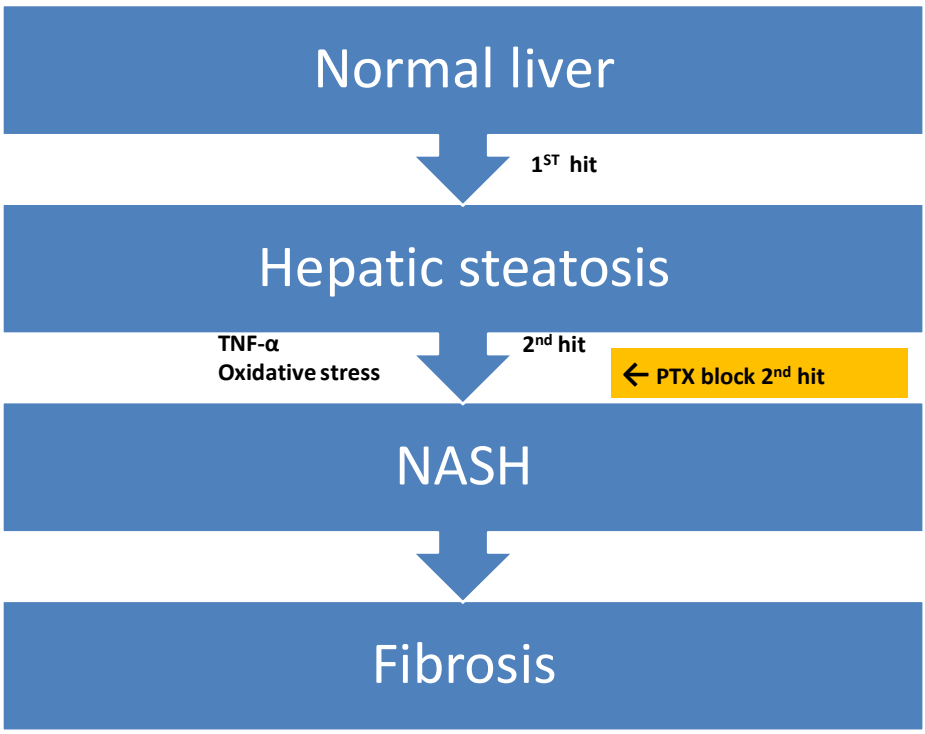

Figure 1. Mechanism of action of Pentoxifylline on NASH

Objectives

General Objective:

1. To observe the effect of pentoxifylline on histological improvement of NASH patient .
2. To observe the effect of lifestyle modification on histological improvement of NASH patient.

Specific Objective

1. To compare the effect of pentoxifylline and lifestyle modification on NAFLD activity score (NAS) in NASH patients.
2. To compare the effect of pentoxifylline and lifestyle modification on Fibrosis score in NASH patients.

Methods

This randomized control trial (RCT) – a prospective interventional study was carried out at Bangabandhu Sheikh Mujib Medical University from January 2013 to December 2015. Ethical clearance for the study was taken from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, prior to the commencement of this study. Twenty seven Patients with biopsy proven NASH were randomized in two groups **:** PL group and L group. PL group (n= 18) received pentoxifylline 400 mg three times daily along with lifestyle modification and L group (n=9) received only lifestyle modification for one year. Lifestyle modification included moderate exercise that is 30 minutes walk a day with hypo caloric diet (1600 Kcal / day). After one year, repeat liver biopsy was repeated. Index and end of study NAFLD activity score and fibrosis score was compared between PL & L groups by a single pathologist to avoid inter observer variation using the scoring system validated by Kleiner et al., 2005.[14] As known, this histology scoring system quantifies necro-inflammatory & steatotic changes (steatosis, lobular inflammation, and ballooning) resulting NAFLD activity scores (NAS) that ranged between 0 and 8. Fibrotic changes were evaluated separately from NAS, ranging from

0 (no fibrosis) to 4 (cirrhosis). Quantitative data were presented as mean ± SD & qualitative data were presented as percentage. All data were analyzed by SPSS (version 20). Qualitative data analyzed by Chi-square test & quantitative data by student's T-test. All quantitative and qualitative data were analyzed between responders and non-responders. The univariate and multi variate logistic regression analysis were done to find out best predictor of patient response. A statistically significant result was considered when *P* value less than 0.05

Operational definition

NASH: NAFLD Activity Score (NAS) in liver biopsy greater than or equal to 5 was considered as NASH.

Non NASH Fatty Liver (NNFL): NAFLD Activity Score (NAS) in liver biopsy less than 5 was considered as Non NASH Fatty Liver (NNFL).

Weight reduction: During one year of study time those patients who lost ≥7% of their body weight was considered as significant weight reduction.

Metabolic syndrome: If patient met three or more of the following five criteria then considered as Metabolic syndrome: (i) Waist circumference in male ≥ 90 cm & in female ≥ 80 cm (ii) TG ≥ 150 mg/dl (iii) HDL in male ≤ 50 mg/dl & in female ≤ 40 mg/dl (iv) Systolic BP ≥ 130 mm of Hg and/or diastolic BP ≥ 85 mm of Hg and/or patient on antihypertensive (v) Fasting blood glucose ≥ 5.6 mmol/L and/or patient on antidiabetic agents .

Histological responder: NAS improvement ≥2 or Fibrosis score improvement ≥ 1 were considered as histological responder.

Histological non-responder: NAS improvement <2 or Fibrosis score improvement < 1 were considered as histological non responder.

Result

A total of 27 patients were included and divided into two groups. Among them, 18 were in PL Group and 9 were in L Group. Mean age of patients were 40.37 ± 10.08 years, 43.94 ± 9.78 years in PL Group and 33.22 ± 6.40 years in L Group (p value 0 .006). Twenty of them were female (74.07 %), 15 (83.3 %) in PL Group & 5 (55.6 %) in L Group (p value 0.13) . According to Asian criteria (BMI ≥25kg/m2 consider as obese), 16 (59.26 %) were obese, 13 (72.2 %) in PL Group & 3 (33.3 %) in L Group (p value 0.05). Total 8 (29.63 %) patients were diabetic, 6 (33.3 %) in PL Group & 2 (22.2 %) in L Group (p value 0.57) . Total 9 (33.33 %) patients were hypertensive, 6 (33.3 %) in PL Group & 3 (33.3 %) in L Group (p value 1) .The baseline liver function tests , fasting blood sugar, insulin resistance index and fasting lipid profile did not differ significantly between two groups. (Table I)

Table 1: Baseline characteristics of patients

Variables	PL Group (mean ± SD)	L group (mean ± SD)	p-value
Age (year)	43.94 ± 9.78	33.22 ± 6.40	0.006
Sex (male/female)	3/15 (16.7%/83.3 %)	4/5(44.4%/55.6%)	0.13
Obesity (yes/no)	13/5 (72.2%/27.8%)	3/6 (33.3%/66.7%)	0.05
Diabetes (yes/no)	6/12 (33.3%/66.7%)	2/7(22.2%/77.8%)	0.57
Hypertension (yes/no)	6/12 (33.3%/66.7%)	3/6 (33.3%/66.7%)	1
BMI (kg/m2)	27.63 ± 3.14	24.36 ± 1.57	0.007
Bilirubin (µmol/L)	9.28 ± 2.52	10.51 ± 3.46	0.30
ALT (U/L)	67.17 ± 37.33	59.67 ± 30.77	0.60
AST (U/L)	47.67 ± 31.59	39.89 ± 18.90	0.50
GGT (U/L)	65.83 ± 50.18	53.00 ± 19.33	0.47
ALP (U/L)	103.65± 28.18	84.57 ± 42.95	0.21
FBS (mmol/L)	5.30 ± 0.99	5.41 ± 2.06	0.86
HOMA- IR	2.21 ± 1.50	2.06 ± 1.68	0.82
Cholesterol (mg/dl)	191.06 ± 56.66	203.22 ± 50.78	0.59
LDL (mg/dl)	105.93 ± 49.35	119.00 ± 31.95	0.51
HDL (mg/dl))	37.76 ± 9.93	34.78 ± 14.71	0.54
Triglycerides (mg/dl)	219.76 ± 147.24	315.00 ± 272.4	0.71

In PL group, mean NAFLD Activity Score (NAS) improvement at the end of study was 2.44 ± 1.62, whereas, in L group it was 0.89 ± 1.05. The difference of NAS improvement between PL and L group was statistically significant (p=0.01). In PL group, mean Fibrosis Score improvement was -0.17 ± 0.98, whereas, in L group it was 0.00 ± 0.71. The difference of Fibrosis Score improvement between PL and L group was not statistically significant (p=0.66) (Table II).

The mean BMI improvement in PL group was 1.40 ± 2.05 kg/m^2 and in L group was 0.45 ± 1.35 kg/m^2. Mean difference of BMI improvement between PL and L group was not statistically significant (p=0.22). The mean Waist Circumference (WC) improvement in PL group was 3.00 ± 3.86 cm and in L group was 1.00 ± 3.61 cm. Mean difference of WC improvement between PL and L group was not statistically significant (p=0.21) (Table II).

Table II: Dynamic characteristic improvement

Improvement	PL group (mean ± SD)	L group (mean ± SD)	P value
NAS	2.44 ± 1.62	0.89 ± 1.05	0.01
Fibrosis Score	-0.17 ± 0.98	0.00 ± 0.71	0.66
BMI (kg/m^2)	1.40 ± 2.05	0.45 ± 1.35	0.22
WC (cm)	3.00 ± 3.86	1.00 ± 3.61	0.21
TG (mg/dl)	39.81 ± 150.25	- 44.75 ± 191.90	0.25
Cholesterol (mg/dl)	1.62± 63.78	-10.00 ± 102.55	0.73
HDL (mg/dl)	3.14 ± 7.78	-9.4 ± 22.85	0.08
LDL (mg/dl)	-3.86 ± 61.47	17.29 ± 26.47	0.40
FBS (mmol/l)	-0.09 ± 0.84	0.005 ± 1.90	0.86
HOMA- IR	0.22± 2.10	0.97 ± 1.63	0.45
ALT (U/L)	35.72± 38.21	27.11± 30.26	0.56
GGT (U/L)	25.24 ± 37.73	-2.67± 53.87	0.13

Considering NAS ≥ 2 or Fibrosis ≥ 1 as responders, total 17 patients were responder and 10 patients were non-responder. Among the 17 responders, 14 patients were in PL group (82.4% of PL group) and 3 patients were in L group (33.33% of L group); whereas, among the 10 non-responder 4 patients were in PL group (22.22% of PL group) and 6 patients were in L group (66.67 % of L group). The difference of response between PL and L group was significant (p value 0.02). The overall NAS improvement in responder was 2.82 ± 1.18 and in non-responder was 0.40 ± 0.97. Overall Fibrosis score improved 0.12± 0.93 in responder and -0.50 ± 0.71 in non-responder (Table III).

The mean baseline BMI in responders were 26.64 ± 3.19 kg/m^2 and 26.37 ± 3.11 kg/m^2 in non-responders (p value 0.669).

Baseline metabolic characteristics such as obesity and components of metabolic syndrome i.e. diabetes and hypertension had no significant effect on patients' response. Total 9 patients lost ≥ 7% weight. Among them, 66.67 % were histological responders and 33.33 % were histological non-responders. On the other hand those who did not lose 7% weight, 61.11 % were histological responders and 38.89 % were histological non-responders. So, significant weight loss (7% or more) was not associated with significant histological improvement (p value 0.79).

Table III: Factors associated with response

Factors	Responder (n=17) (mean ± SD)	Non- responder (n=10) (mean ± SD)	P value
Baseline factors:			
Category of patient (treatment/control)	14/3(82.4%/17.6%)	4/6(40%/ 60%)	0.02
BMI (kg/m^2)	26.64 ± 3.19	26.37 ± 3.11	0.84
Obesity (yes/no)	9/8 (52.9%/47.1%)	7/3 (70%/30%)	0.40
Hypertension (yes/no)	5/12 (29.4%/70.6%)	4/6(40%/60%)	0.59
Diabetes (yes/no)	5/12 (29.4%/70.6%)	4/6 (40%/60%)	0.97
Dynamic factors			
NAFLD Activity Score improvement	2.82 ± 1.18	0.40 ± 0.97	0.000
Fibrosis Score improvement	0.12 ± 0.93	-0.50± 0.71	0.08
BMI improvement (kg/m^2)	1.29 ± 1.85	0.74 ± 1.97	0.48
Weight reduction 7% or more (yes/no)	6/11 (35.29 %/64.71 %)	3/7 (30%/70%)	0.79
FBS improvement (mmol/l)	-0.10± 0.82	-0.004 ± 1.81	0.85
2HABF improvement (mmol/l)	-0.08 ± 2.85	0.60 ± 1.71	0.46
IRI improvement	0.46 ± 1.99	0.40 ± 2.06	0.95
TG improvement (mg/dl)	45.29 ± 161.22	-35.50 ± 169.50	0.25
Cholesterol improvement (mg/dl)	-5.29 ± 67.61	2.00 ± 91.65	0.82
LDL improvement (mg/dl)	-9.08 ± 64.16	19.56 ± 27.20	0.23
HDL improvement (mg/dl)	4.08 ± 8.50	-6.00 ± 17.98	0.12

Logistic regression analysis was done to find out best predictor of patient response. Important dynamic factors as well as 'Treatment group' were considered for logistic regression analysis. Univariate analysis showed only 'treatment group' as a significant predictor (p=0.03; OR=7.00, CI=1.18-41.36) of patient response. Other factors such as, BMI improvement (p=0.46), HOMA-2 IR improvement (p=0.95) could not predict patient response significantly (Table III). Multivariate logistic regression analysis was done considering to see the effects of all confounding variable together. Multivariate analysis also showed that, only 'treatment group' significantly predict patient

response (p value 0.04; OR=18.71, CI=1.03-340.13). So, both univariate and multivariate analysis revealed only 'Treatment group' as a predictor for patient response (Table IV).

Table IV: Predictors of patient response

Predictors	Univariate Analysis		Multivariate Analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Category of patient (treatment)	0.03	7.00 (1.18-41.36)	0.04	18.71 (1.03-340.13)
BMI improvement	0.46	1.18(0.75-1.86)	0.30	0.66 (0.30-1.45)
HOMA-2 IR improvement	0.95	1.02 (0.63-1.64)	0.33	1.36 (0.73-2.55)

Probable side effects

Any adverse events that occurred during patient management were considered as side effect of drugs. Most of them occurred both in PL group and L group. Most common side effects were abdominal pain and dyspepsia. In PL group 4 patients (22.22%) developed abdominal pain , whereas, in L group three patients (33.33%) developed abdominal pain (p value 0.55) (Table 5). On the other hand, 2 patients (11.11%) in PL group and two patients (22.22%) in L group had dyspepsia (p value 0.46) (Table V). The occurrence of all possible side effects in PL and L group, could not reach statistically significant level. No patient required treatment discontinuation after development of side effects.

Table V: Probable side effects

Side effects	PL group(n=18)	L group(n=9)	P value
Abdominal pain(Y/N)	4/14	3/6	0.55
Diarrhoea(Y/N)	0/18	0/9	0
Dyspepsia(Y/N)	2/16	2/7	0.46

Discussion

This prospective randomized control trial was conducted in Hepatology department of BSMMU, Dhaka from January 2013 to December 2015. In this study 18 NASH patients were randomly selected in whom Pentoxifylline plus lifestyle modification was given and 9 NASH patients in whom only life style modification was given for one year . After one year, liver biopsy was repeated and compared between index and end of study liver biopsy. Current study prospectively showed that Pentoxifylline significantly improved histology of NASH patient compared to control group.

The assessment of therapeutic response for NASH is a complex process. As there is no validated biomarkers of therapeutic response, one must rely on histological assessment. The activity score for nonalcoholic fatty liver disease quantifies the severity of steatosis, hepatocellular ballooning, and lobular inflammation, the key histologic components of the disease.[15] A decrease in their severity occurs with amelioration of the disease; however, the severity of these components (especially hepatic steatosis) may also decrease with progression of fibrosis to cirrhosis.[16] So, both NAFLD Activity Score (NAS) and Fibrosis Score were taken in consideration as significant hislogical improvement in this study .

Sanyal et al,[17] in 2010 showed in a large RCT that Vitamin E had significant role in histological improvement of NASH patient. That RCT revealed, Vitamin E improved NAS $\geq$ 2 in 43% of patient. Georgescu et al,[18] in 2009 showed in a RCT that Telmisartan

seem to be efficient in hypertension associated NASH. This RCT revealed that, Pentoxifylline improved NAS ≥ 2 in 75% of patient. So, regarding improvement of NAFLD Activity Score (NAS) Pentoxifylline is more efficacious than Telmisartan and Vitamin E (Sanyal et al,[17] in 2010, Georgescu et al,[18] 2009) .

Musso et al,[19] in 2010, in a meta-analysis showed that weight reduction through life style modification had significant effect on histological improvement of NASH patient. But meta-analysis could not quantify about the cut off value of weight reduction in which steatosis or NAFLD Activity Score improved. Weight reduction more than 7% sustained over 48 weeks is associated with significant reduction in histological severity of NASH.[20] As life style modification is the standard approach of patient management, current study included this approach both in treatment and control groups.

In current study, 7% or more body weight reduced in 9 out of 27 patients. Among them 6 (66.67%) had significant histological improvement, whereas, 3 of them (33.33%) had no significant histological improvement. On the other hand, 18 patients did not lose weight 7% or more; between them 11 patients (61.11%) had significant histological improvement and 7 patients (38.89%) had no significant histological improvement. So, 7% or more weight loss, did not affect significantly in patients response (p value 0.79) (Table III). These findings were not consistent with Wagner et al.,[21] 2011 where weight loss correlated with histological improvement. The underlying cause was not clear, but these findings further strengthen that the histological improvements of Pentoxifylline were not associated with significant weight reduction.

In current study, others bio-chemical parameter such as FBS, 2HABF, HOMA 2-IR, ALT, GGT, Cholesterol, TG, HDL and LDL improvement did not differ significantly among histological responders and non-responders. These findings revealed that bio-chemical improvement did not correlate with histological improvement

Regarding safety profile it revealed that, Pentoxifylline had minimum side effects. These include abdominal pain and dyspepsia. But these events occurred both in treatment and control group. None required treatment discontinuation due to side effect. This finding was consistent with Wagner et al,[21] 2011 where adverse events were mild and most frequently abdominal cramp and were similar in both groups.

Conclusion

This Randomized Control Trial revealed that Pentoxifylline improved significantly overall histology of NASH patients. The histological improvement of Pentoxifylline were independent of weight reduction and improvement of BMI, blood glucose, IRI and lipid profile. Its therapeutic effect was unaltered irrespective of metabolic factors such as diabetes, hypertension, dyslipidemia, obesity or metabolic syndrome. Pentoxifylline was safe and effective in NASH patients. Based on the current study results, it can be concluded that Pentoxifylline significantly improves histology of NASH patients

References

1. Angulo P, Hui JM, Marchesini. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007; 45: 846-54
2. Browning JD, Szezepaniak LS, Dobbins R. Prevalence of hepatic steatosis in an urban population in the united states. Am J Gastroenterol. 2003; 98:960-67
3. Grattagliano I, Portineasa P, Palmieri VO. Managing nonalcoholic fatty liver disease:recommendations for family physicians.Can Fam physician. 2007; 53:857-63
4. Powell EE, Cooksley WG, Hanson R. The natural history of nonalcoholic steatohepatitis:a follow up study of forty two patients for upto 21 years. Hepatology. 1990; 11:74-80.
5. Adams LA, Lymp JF, St Sauver J. The natural history of nonalcoholic fatty liver disease: a population –based Cohort study. Gastroenterology. 2005; 129:113-121.
6. Abiru S, Migita K, Maeda Y, Daikoku M, Ito M, Ohata K, Nagaoka S, Matsumoto T, TakiiY, Kusumoto K, Nakamura M, Komori A, Yano K, Yatsuhashi H, Eguchi K, Ishibashi H. 2006 ,‘ Serum cytokine & soluble cytokine receptor levels in patients with nonalcoholic steatohepatitis. Liver Int. 2006; 26:39-45
7. Perseghin G, Petersen K, Shulman GI. Cellular mechanism of insulin resistance:Potential links with inflammation. Int J obesRelatMetabDisord. 2003; 27(Suppl 3):S 6-S11
8. Choi S, Diehl AM. Role of inflammation in nonalcoholic steatohepatitis. CurropinGastroenterol. 2005; 21:702-707
9. Tilg H, Diehl AM. 2000 ,‘Cytokines in alcoholic & nonalcoholic steatohepatitis. N Eng J Med. 2000; 343:1467-76[Pub Med:9506740]
10. Strieter RM, RemickDG,WardPA,Spengler RN, Lynch JP, Larrick J. Cellular & molecular regulation of tumour necrosis factor–alpha production by pentoxifylline. Int J Immunopharmacol. 1996; 18:739-748.
11. Koppe SW, Sahai A, Malladi P, Whittington PF, Green RM. Pentoxifylline attenuates steatohepatitis induced by the methionine choline deficient diet. J Hepatol 2004; 41:592-598.
12. Bhat VB, Madyastha KM. Antioxidant and radical scavenging properties of 8-oxo derivatives of xanthine drugs pentoxifylline and lisofylline. BiochemBiophys Res Commun 2001; 288:1212-1217
13. Radfar M, Larijani B, HadjibabaieM,Rajabipour B, MojtahediA,Abdollahi M 2005 ,‘Effects of pentoxifylline and oxidative stress and levels of EGF and NO in blood of diabetic type -2 patients; a randomized ,double blind placebo-controlled trial ,’Biomed pharmacother. ; 59:302-306.
14. Kleiner DE, Brunt EM,Van Natta M,Behling C. Design & validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41:1313-1321
15. Adams LA, Talwalkar JA., 2006 , ‘Diagnostic evaluation of nonalcoholic fatty liver disease. J ClinGastroenterol; 2006; 40(Suppl1):S34-8
16. Bacon BR, Farahvash MJ, Janney CG. Nonalcoholic steatohepatitis: an expanded clinical entity ,’Gastroenterology ; 107: 1103-09
17. Sanyal AJ, Chalasni N, Kowdley KV. Pioglitazone,vitamin E or placebo for nonalcoholic steatohepatitis. N Eng J Med. 2010; 362(18):1675-1685[Pub Med:20427778]
18. Georgescu EF, Ionescu R, Niculescu M. Angiotensin-receptor blockers as therapy

for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. World J Gastroenterol. 2009; 15(8): 942-954.
19. Musso G, Gambino R, Cassader M. 2010 A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology. 2010; 52(1): 79-104
20. Promrat K, Kleiner DE, Niemeier HM. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010; 51:121-129.
21. Van Wagner LB, Koppe SW, Brunt EM, Gottstein J, Gardiki-otes K, Green RM, Rinella ME. Pentoxifylline for the treatment of non-alcoholic steatohepatitis: a randomized controlled trial. Ann Hepatol. 2011; 10: 277-286