World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/2150-5349office
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v2.i1.1

World J Gastrointest Pharmacol Ther 2011 February 6; 2(1): 1-5
ISSN 2150-5349 (online)

EDITORIAL

Is there any progress in the treatment of non-alcoholic fatty liver disease?

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Received: June 26, 2010 Revised: December 15, 2010
Accepted: December 22, 2010
Published online: February 6, 2011

Abstract

Despite the fact that non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis, are becoming increasingly prevalent in the industrialised countries, there are no licensed pharmacological treatments for them. Weight loss and life modifications, antioxidant therapies and insulin-sensitising agents are the current treatment strategies and have all been tested with inconclusive results. Low sample numbers, inadequate treatment duration and invalid surrogate markers for treatment response might all account for these results. As NAFLD is a systemic rather than a liver disease, future trials should address the patient as a whole and also address cardiovascular risk factors.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Weight loss; Pioglitazone; Metformin

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Tsochatzis EA, Papatheodoridis GV. Is there any progress in the treatment of non-alcoholic fatty liver disease? *World J Gastrointest Pharmacol Ther* 2011; 2(1): 1-5 Available from: URL: http://www.wjgnet.com/2150-5349/full/v2/i1/1.htm
DOI: http://dx.doi.org/10.4292/wjgpt.v2.i1.1

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and its severe clinical form, non-alcoholic steatohepatitis (NASH), are becoming increasingly prevalent in industrialised countries, along with the epidemic of obesity[1]. The prevalence of NAFLD is estimated to be 10%-25% in the Western world, while the corresponding prevalence of NASH ranges from 2%-7%[2-16](Table 1). Insulin resistance and metabolic syndrome have been implicated both in the pathogenesis and disease progression of NAFLD[17-19], causing, among other symptoms, increased free fatty acid influx to the liver, oxidative stress, mitochondrial toxicity, deregulation of adipokines and subsequently inflammation and fibrosis[20-22](Figure 1). It has become clear that NAFLD is not a benign non-progressive disease, as originally suggested, but results in increased morbidity and mortality, as shown in several studies with longitudinal follow-up[23-25]. It is notable that cardiovascular events and non liver-related deaths were the main cause of mortality in patients studied[24,25]. This is not surprising given the high prevalence of metabolic syndrome and its components in NAFLD patients. Currently, there are no licensed therapies for NAFLD, despite the abundance of clinical trials. In this review we will explore the current status of such treatments and propose a future research agenda.

TREATMENT STRATEGIES FOR NAFLD

The existing treatment strategies for NAFLD can be divided into three main categories: weight loss and life-style modifications, insulin-sensitising agents and antioxidant therapies. As a general comment, most studies suffer from inadequate patient numbers, lack of randomisation and use of markers for treatment response other than histology. It

Table 1 Prevalence of non-alcoholic fatty liver disease in different countries

Author	Country	Population	*n*	Prevalence of NAFLD (%)	Methods of diagnosis
Fan *et al*[5] , 2007	China	Normal	14646	14	US
Papatheodoridis *et al*[8] , 2007	Greece	Normal	3063	18	Liver enzymes
Zelber-Sagi *et al*[16] , 2006	Israel	Normal	326	30	US
Bedogni *et al*[3] , 2007	Italy	Normal	598	20	US
Targher *et al*[12] , 2007	Italy	T2DM	2839	70	US
Sorrentino *et al*[11] , 2004	Italy	Bariatric surgery	80	72	Biopsy
Hamaguchi *et al*[6] , 2005	Japan	Normal	4401	18	US
Yamamoto *et al*[15] , 2007	Japan	Normal	263	18	US
Park *et al*[9] , 2006	Korea	Normal	6648	19	US
Roesch-Dietlen *et al*[10] , 2006	Mexico	Metabolic syndrome	337	16	US
Browning *et al*[4] , 2004	USA	Normal	2287	31	MRS
Tran *et al*[13] , 2006	USA	Living donors	70	38.5	Biopsy
Kunde *et al*[7] , 2005	USA	Bariatric surgery	233	97	Biopsy
Weston *et al*[14] , 2005	USA	Chronic liver disease	742	39	US/CT

NAFLD: Non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; US: Ultrasonography, MRS: Magnetic resonance spectroscopy; CT: Computerized tomography.

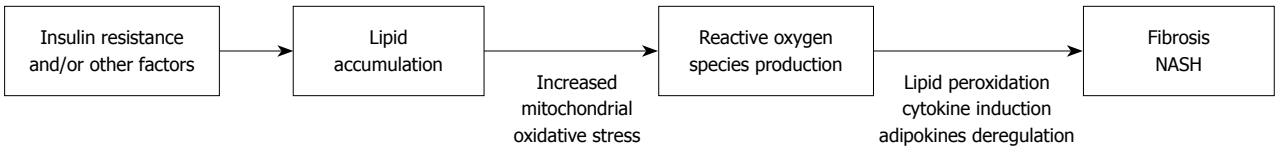

Figure 1 Mechanisms of progression from normal liver to non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. NASH: Non-alcoholic steatohepatitis.

is not, therefore, surprising that they are often inconclusive and fail to show any treatment effect. Currently, there is no licensed pharmacological treatment for NASH and patients are usually advised to lose weight and exercise.

Weight loss

As NAFLD is most commonly associated with obesity[26], weight loss is a reasonable initial step towards treating this condition. The theoretical advantages of weight loss include decreasing insulin resistance and, if combined with exercise, increasing muscle insulin sensitivity. Despite the pathophysiological evidence of such an approach, there has been only one randomised control trial (RCT) of weight loss in patients with NAFLD, with a sample size of just 31 patients[27]. Patients in the intervention group were targeted for a 7%-10% weight reduction through intensive lifestyle intervention and were monitored for a year with initial and end-of-treatment liver biopsies. Although there was significant improvement in the NASH histological activity score (NAS) in the intervention group and a significant correlation of percent weight loss with improvement in NAS, no significant improvement in fibrosis was documented[27]. All other trials have been non-randomised, with no control group and have usually comprised selected patients or case series[28]. However, improved liver biochemistry and even resolution of stigmata of liver disease have been shown with weight loss in selected overweight patients[29,30]. The main concerns with this strategy include the feasibility of maintaining weight loss over a prolonged time course. Furthermore, rapid weight loss in morbidly obese can actually worsen fibrosis[31]. Therefore, counselling should aim towards gradual weight loss with appropriate life-style modifications and behavioural therapies that would allow weight loss to be maintained over the course of time[28].

Orlistat, which is a reversible inhibitor of gastric and pancreatic lipase and thus prevents the absorption of diet triglycerides, is used for weight loss and has been tested in the management of NASH in a small RCT[32]. Although patients who achieved a weight loss of > 9% improved in biochemistry and inflammation measures, there were no significant differences in weight loss between the orlistat and the placebo group.

Bariatric surgery is normally limited to morbidly obese patients and is considered as a therapeutic option in selected patients with NASH[33]. However, the recent Cochrane metanalysis found that evidence on the potential benefits and risks of bariatric surgery is derived from cohort studies and is, therefore, not conclusive[34].

It should be also underlined that in addition to food quantity, quality also matters. Results from cohort studies suggest that patients with NAFLD have higher consumption of saturated fatty acids and cholesterol, higher consumption of soft drinks that contain fructose and lower consumption of vitamins A and E[35-38]. Therefore, counselling regarding the quality of calories consumed should also be offered. Lipid lowering therapies are safe in patients with liver disease[39] and preliminary evidence suggests that they might prove beneficial in patients with NAFLD[40].

Anti-oxidant therapies

Ant-oxidant therapies have been tried for NAFLD on the theoretical basis that oxidative stress is involved in the pathogenesis of the disease. The results of trials are inconclusive and contradictory, probably because of the small patient numbers. A small pilot trial of pentoxifylline showed improvement in aminotransferases in the 11 patients who completed the 1-year course of medication, although no follow-up histological evaluation was available[41]. Ursodeoxycholic acid failed to show any benefit after two years of therapy in a RCT of 165 patients[42]. A combination of vitamins E and C taken for 6 mo improved fibrosis but not necroinflammation or liver enzymes[43]. A recent RCT, published in abstract form, of vitamin E or pioglitazone or placebo, showed significant improvement in the NAS score of patients who received vitamin E compared to the other two groups.However, no improvement in fibrosis was documented[44]. However, other small RCTs have failed to demonstrate any treatment effect of vitamin E[45,46].

Insulin-sensitising therapies

As insulin resistance is considered the main underlying mechanism and predisposing condition for NASH, treatment strategies targeting insulin resistance are a main focus of the current research agenda. Metformin and thiazolidinediones which are licensed antidiabetic medications that target peripheral and hepatic insulin resistance have been used in the treatment of patients with NASH.

The first evidence of the potential effect of metformin came from a small cohort study of 20 patients with no follow-up histological evaluation, in which transaminase values and insulin sensitivity improved after 4 mo of treatment[47]. A small Turkish RCT of 36 patients, comparing metformin with no treatment and with 6 mo follow up, confirmed the improvement in transaminases but failed to demonstrate any effect on liver histology[48]. An RCT of metformin *vs* vitamin E *vs* no treatment in patients who were all assigned to prescriptive diet showed a significantly higher rate of transaminase normalization as well as a significant improvement in necroinflammation and fibrosis compared to baseline biopsy in the metformin group[45]. However, liver biopsy was not performed in the control group and it is thus difficult to assess if the histological improvement was due to weight loss or metformin. Therefore, although metformin is a safe and promising medication, it has not yet been assessed in properly designed and adequately powered RCTs.

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-γ agonists that improve insulin resistance in liver, muscle and adipose tissue. The licensed TZDs, pioglitazone and rosiglitazone, have been both tried in RCTs in patients with NAFLD. The two drugs appear to have different effects on lipid metabolism, as rosiglitazone has no effect on de novo hepatic lipogenesis and plasma triglycerides, while pioglitazone actually decreases both[49]. An RCT of 45 mg of pioglitazone *vs* placebo for 6 mo, showed significant improvements in steatosis, necroinflammation and ballooning in the treatment group although improvement in fibrosis did not reach statistical significance ($P = 0.008$)[50]. These encouraging results provided the rational for further RCTs of longer duration. A lower dose of pioglitazone (30 mg/d) improved fibrosis and hepatocellular injury compared to placebo in an RCT of 74 non-diabetic patients with NASH. However, the biggest RCT to date, with a follow-up of 2 years, failed to show any significant histological improvement in the pioglitazone group (30 mg/d) compared to the placebo group[44]. RCTs on rosiglitazone, of one and two year duration, have shown no significant effects on liver histology[51,52].

CRITICAL APPRAISAL AND FUTURE DIRECTIONS

Although NAFLD is an increasingly prevalent disease, there is a lack of approved therapies for it. There are several reasons for this absence of effective therapies.

Firstly, most published studies are not adequately powered to demonstrate significant treatment effects and some of the non-significant findings that they report might actually be type Ⅱ errors.

Secondly, treatment effects are assessed after 6 or 12 mo of therapy duration, which is an arbitrary time cut-off and might be inadequate. Although such treatment durations have been successfully implemented for chronic viral hepatitis B and C infections, these conditions have totally different pathophysiology of liver injury and probably a more rapid clinical course than NAFLD[25,53].

Thirdly, the NAS activity score is increasingly being used as a surrogate marker to assess therapeutical effect. However, this score is not a valid surrogate marker for NAFLD as it does not take fibrosis into account[54]. Existing studies suggest that the presence and severity of fibrosis actually dictate long-term mortality in patients with NAFLD[25], while the NAS score is an untested, if not irrelevant, surrogate marker[55]. Therefore, although improvements in the NAS score not accompanied by improvements in fibrosis would currently classify a study as having a positive result, the true value of these studies is unknown.

Fourthly, metformin remains an untested therapeutic option, despite preliminary evidence of its benefits. This may be because it is a cheap and weel established drug and there is, therefore, limited interest in funding and any RCT would have to be investigator-initiated.

Lastly, and most importantly, NAFLD is a systemic rather than a liver disease.Indeed, cardiovascular disease is the main cause of death in NAFLD patients[24]. Therefore, all risk factors should be globally assessed and therapeutic strategies should ideally target the patient as a whole rather than liver-specific disease manifestations alone.

Future trials should recruit larger number of patients for a longer treatment period. The recent pioglitazone or vitamin E for nonalcoholic steatohepatitis RCT demonstrated that insulin resistance might not be the driving force behind fibrosis progression in NAFLD patients and that combination therapy targeting different mechanisms might represent the optimal strategy for NAFLD[44]. Angiotensin

receptor blockers and angiotensin converting enzyme inhibitors have shown experimental evidence of effect and are already tested in ongoing RCTs[56]. Other potential future treatments include incretin analogues, silymarin, dietary factors such as omega-3 fatty acids and polyunsaturated fatty acids and even molecular targets[56,57]. As evidence is constantly accumulating, it is a matter of time before effective treatments for NAFLD become available.

REFERENCES

1 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231
2 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112
3 **Bedogni G**, Miglioli L, Masutti F, Castiglione A, Crocè LS, Tiribelli C, Bellentani S. Incidence and natural course of fatty liver in the general population: the Dionysos study. *Hepatology* 2007; **46**: 1387-1391
4 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395
5 **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**: 663-668
6 **Hamaguchi M**, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005; **143**: 722-728
7 **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**: 650-656
8 **Papatheodoridis GV**, Goulis J, Christodoulou D, Manolakopoulos S, Raptopoulou M, Andrioti E, Alexandropoulos N, Savvidou S, Papachristou A, Zervou E, Seferiadis K, Kousidou P, Vogiatzakis E, Tsianos E. High prevalence of elevated liver enzymes in blood donors: associations with male gender and central adiposity. *Eur J Gastroenterol Hepatol* 2007; **19**: 281-287
9 **Park SH**, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, Sung IK, Sohn CI, Keum DK, Kim BI. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *J Gastroenterol Hepatol* 2006; **21**: 138-143
10 **Roesch-Dietlen F**, Dorantes-Cuéllar A, Carrillo-Toledo MG, Martínez-Sibaja C, Rojas-Carrera S, Bonilla-Rojas QC, Uchino-Higueras V, Lagunas T, Carrasco-Arróniz MA, Soler-Leal B, León-Valdivieso J, Cid-Juárez S, Martínez JA. [Frequency of NAFLD in a group of patients with metabolic syndrome in Veracruz, Mexico]. *Rev Gastroenterol Mex* 2006; **71**: 446-452
11 **Sorrentino P**, Tarantino G, Conca P, Perrella A, Terracciano ML, Vecchione R, Gargiulo G, Gennarelli N, Lobello R. Silent non-alcoholic fatty liver disease-a clinical-histological study. *J Hepatol* 2004; **41**: 751-757
12 **Targher G**, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; **30**: 1212-1218
13 **Tran TT**, Changsri C, Shackleton CR, Poordad FF, Nissen NN, Colquhoun S, Geller SA, Vierling JM, Martin P. Living donor liver transplantation: histological abnormalities found on liver biopsies of apparently healthy potential donors. *J Gastroenterol Hepatol* 2006; **21**: 381-383
14 **Weston SR**, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, Terrault NA. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. *Hepatology* 2005; **41**: 372-379
15 **Yamamoto K**, Takada Y, Fujimoto Y, Haga H, Oike F, Kobayashi N, Tanaka K. Nonalcoholic steatohepatitis in donors for living donor liver transplantation. *Transplantation* 2007; **83**: 257-262
16 **Zelber-Sagi S**, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. *Liver Int* 2006; **26**: 856-863
17 **Tsochatzis E**, Papatheodoridis GV, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008; 27: 80-89
18 **Tsochatzis EA**, Manolakopoulos S, Papatheodoridis GV, Archimandritis AJ. Insulin resistance and metabolic syndrome in chronic liver diseases: old entities with new implications. *Scand J Gastroenterol* 2009; **44**: 6-14
19 **Marchesini G**, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923
20 **Tsochatzis EA**, Papatheodoridis GV, Archimandritis AJ. Adipokines in nonalcoholic steatohepatitis: from pathogenesis to implications in diagnosis and therapy. *Mediators Inflamm* 2009; **2009**: 831670
21 **Pessayre D**, Fromenty B. NASH: a mitochondrial disease. *J Hepatol* 2005; **42**: 928-940
22 **Tsochatzis E**, Papatheodoridis GV, Archimandritis AJ. The evolving role of leptin and adiponectin in chronic liver diseases. *Am J Gastroenterol* 2006; **101**: 2629-2640
23 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121
24 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873
25 **Söderberg C**, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology* 2010; **51**: 595-602
26 **Machado M**, Cortez-Pinto H. Non-alcoholic steatohepatitis and metabolic syndrome. *Curr Opin Clin Nutr Metab Care* 2006; **9**: 637-642
27 **Promrat K**, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava JL, Wing RR. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 121-129
28 **Bellentani S**, Dalle Grave R, Suppini A, Marchesini G. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. *Hepatology* 2008; **47**: 746-754
29 **Palmer M**, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology* 1990; **99**: 1408-1413
30 **Ueno T**, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, Torimura T, Inuzuka S, Sata M, Tanikawa K. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997; **27**: 103-107
31 **Andersen T**, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol* 1991; **12**: 224-229
32 **Harrison SA**, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. *Hepatology* 2009; **49**: 80-86
33 **Younossi ZM**. Review article: current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008; **28**: 2-12
34 **Chavez-Tapia NC**, Tellez-Avila FI, Barrientos-Gutierrez T,

Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. *Cochrane Database Syst Rev* 2010; CD007340
35 **Cortez-Pinto H**, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME. How different is the dietary pattern in non-alcoholic steatohepatitis patients? *Clin Nutr* 2006; **25**: 816-823
36 **Musso G**, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, Fagà E, Silli B, Pagano G. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. *Hepatology* 2003; **37**: 909-916
37 **Musso G**, Gambino R, De Michieli F, Biroli G, Premoli A, Pagano G, Bo S, Durazzo M, Cassader M. Nitrosative stress predicts the presence and severity of nonalcoholic fatty liver at different stages of the development of insulin resistance and metabolic syndrome: possible role of vitamin A intake. *Am J Clin Nutr* 2007; **86**: 661-671
38 **Ouyang X**, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, Johnson RJ, Abdelmalek MF. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol* 2008; **48**: 993-999
39 **Chalasani N**, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology* 2004; **126**: 1287-1292
40 **Kimura Y**, Hyogo H, Yamagishi S, Takeuchi M, Ishitobi T, Nabeshima Y, Arihiro K, Chayama K. Atorvastatin decreases serum levels of advanced glycation endproducts (AGEs) in nonalcoholic steatohepatitis (NASH) patients with dyslipidemia: clinical usefulness of AGEs as a biomarker for the attenuation of NASH. *J Gastroenterol* 2010; **45**: 750-757
41 **Adams LA**, Zein CO, Angulo P, Lindor KD. A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. *Am J Gastroenterol* 2004; **99**: 2365-2368
42 **Lindor KD**, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, Lymp JF, Burgart L, Colin P. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *Hepatology* 2004; **39**: 770-778
43 **Harrison SA**, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2003; **98**: 2485-2490
44 **Sanyal AJ**. A randomized controlled trial of pioglitazone or vitamin E for nonalcoholic steatohepatitis (PIVENS). *Hepatology* 2009; **50** (Suppl 1): LB4
45 **Bugianesi E**, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, David E, Rizzetto M, Marchesini G. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 2005; **100**: 1082-1090
46 **Kugelmas M**, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. *Hepatology* 2003; **38**: 413-419
47 **Marchesini G**, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet* 2001; **358**: 893-894
48 **Uygun A**, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, Yesilova Z, Gulsen M, Dagalp K. Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2004; **19**: 537-544
49 **Goldberg RB**, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; **28**: 1547-1554
50 **Belfort R**, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355**: 2297-2307
51 **Ratziu V**, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, Podevin P, Lacorte JM, Bernhardt C, Bruckert E, Grimaldi A, Poynard T. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008; **135**: 100-110
52 **Ratziu V**, Charlotte F, Bernhardt C, Giral P, Halbron M, Lenaour G, Hartmann-Heurtier A, Bruckert E, Poynard T. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. *Hepatology* 2010; **51**: 445-453
53 **Sanyal AJ**, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, Shiffman ML, Heuman D, Coterrell A, Fisher RA, Contos MJ, Mills AS. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006; **43**: 682-689
54 **Gluud C**, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *J Hepatol* 2007; **46**: 734-742
55 **Angulo P**. Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance? *Hepatology* 2010; **51**: 373-375
56 **Vuppalanchi R**, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306-317
57 **Musso G**, Gambino R, Cassader M. Emerging molecular targets for the treatment of nonalcoholic fatty liver disease. *Annu Rev Med* 2010; **61**: 375-392

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