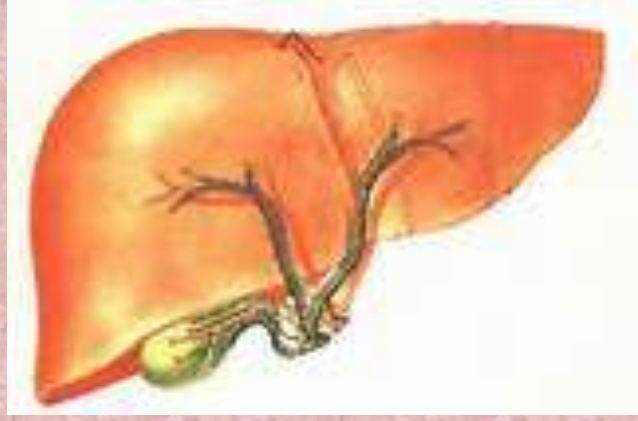
Approccio clinico alla diagnosi e alla terapia del paziente con DM2 e NAFLD o altra epatopatia

Dott.ssa Roberta MANTI

S.C. Malattie Metaboliche e Diabetologia

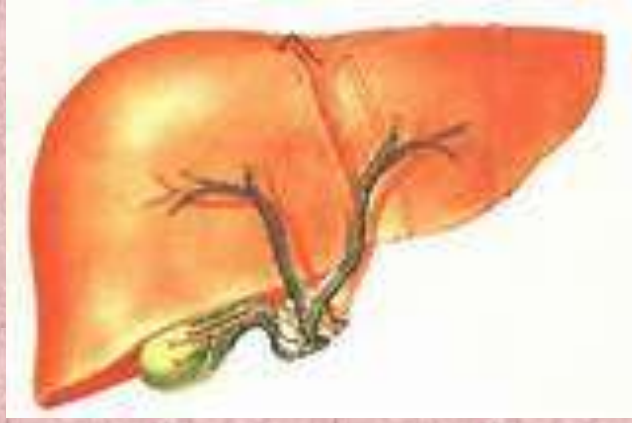
ASLTO5

CASO CLINICO



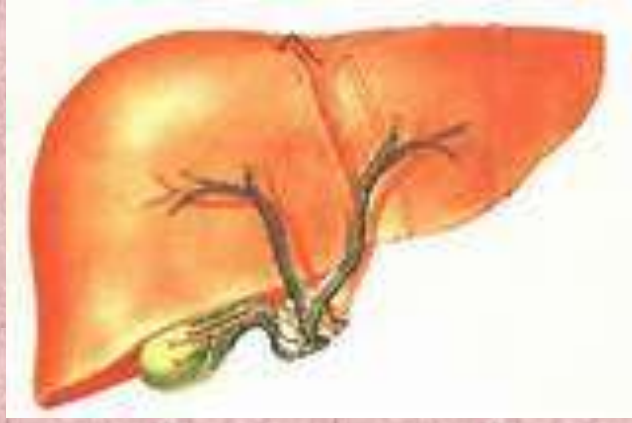
- C.A. maschio 68 anni, BMI:32, CV: 109 cm
- Familiarità positiva per ipertensione e diabete (padre e fratello) ed epatopatia (fratello)
- Idraulico in pensione
- Alimentazione ricca di carboidrati e grassi animali; alcol max 20 gr/die; ex fumatore
- APR: ipertensione dal 1997 in terapia; diabete tipo 2 dal 2011; IRC; pregressa asportazione polipi colon con displasia di basso grado; *dal 2010 riscontro di iperGGT ad andamento oscillante e lieve movimento transaminasi*

CASO CLINICO



- Esami ematochimici disponibili: 2011 => glicata 7,7%, creatinina 1,25 mg%, AST 34 U/l, ALT 40 U/l, GGT: 210 U/l, LDL120 mg%, TG: 187 mg%.
- Ecografia addome: epatomegalia steatosica, margini arrotondati, non lesioni focali, non formazioni litiasiche della colecisti, coledoco nella norma
- RMN A.S.: epatomegalia steatosica senza lesioni focali, VB di norma, non segni stenosi o litiasi

CASO CLINICO

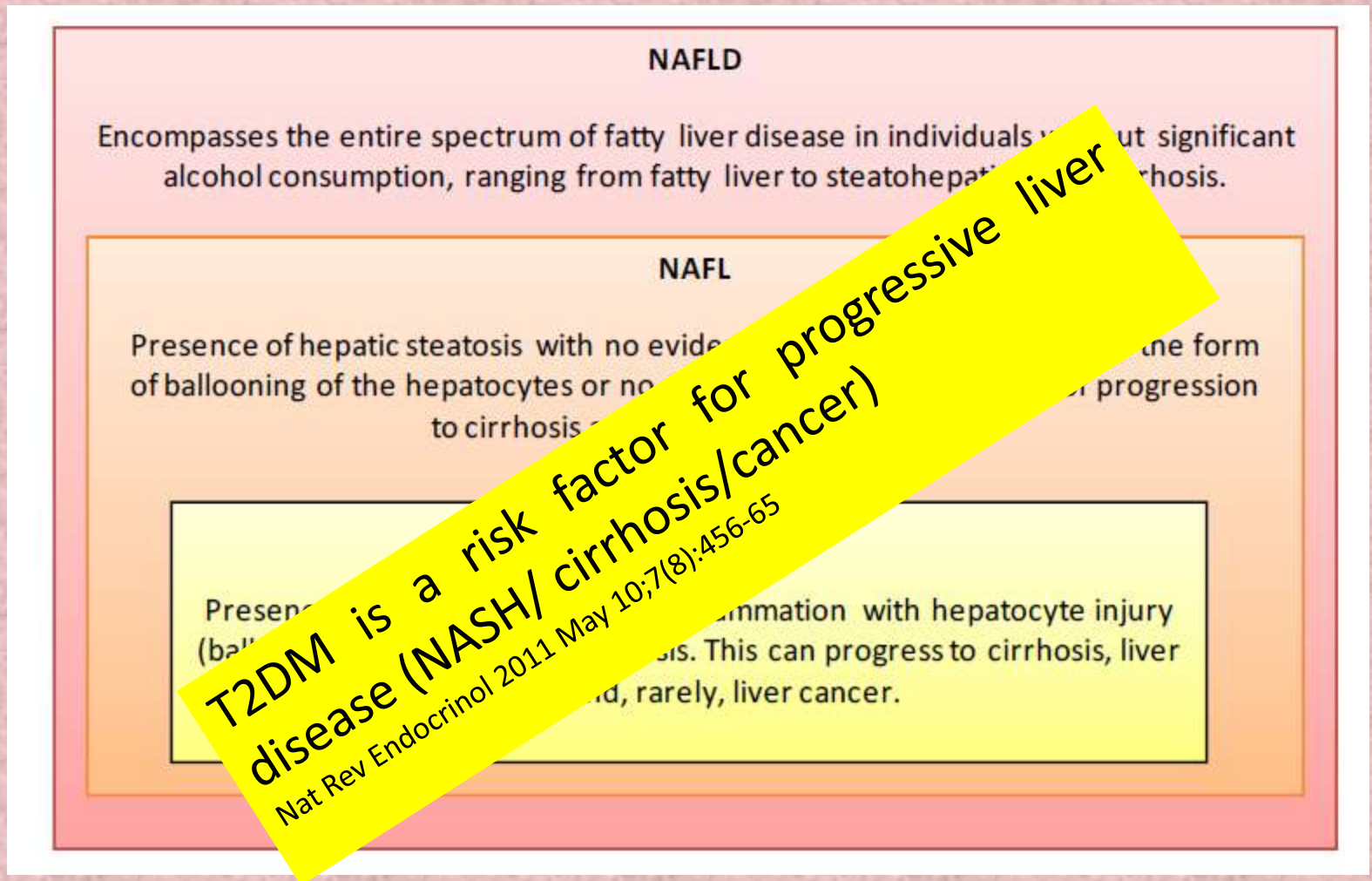


QUALI ESAMI CHIEDERE A QUESTO PAZIENTE PER DEFINIRE IL QUADRO EPATICO?

SPECTRUM OF LIVER DISEASE IN DIABETES

- ABNORMAL LIVER ENZYMES
- CIRRHOSIS
- HEPATOCELLULAR CARCINOMA
- ACUTE LIVER FAILURE
- HEPATITIS C
- NAFLD

K. G. Tolman, Diabetes Care, 2007



T2DM is a risk factor for progressive liver disease (NASH/ cirrhosis/cancer)

Nat Rev Endocrinol 2011 May 10;7(8):456-65

Nutrients **2013**, 5, 4093-4114; doi:10.3390/nu5104093

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

NAFLD

DEFINITION

a. evidence of hepatic steatosi… by hystology)

b. no causes of second… …mulation and no co-existing c… …disease

FULL HISTOLOGICAL SPECTRUM CAN EXIST IN THE PRESENCE OF NORMAL LIVER BIOCHEMISTRY

Diabetic Medicine 2015 Feb 12

HEPATOLOGY, Vol. 55, No. 6, 2012

Table 2. Common Causes of Secondary Hepatic Steatosis

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

>30 gr/die per l'uomo;
>20 gr/die per la donna

Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

HEPATOLOGY, Vol. 55, No. 6, 2012

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Recommendations

7. When evaluating a patient with suspected NAFLD, it is essential to exclude competing etiologies for steatosis and co-existing common chronic liver disease. (Strength – 1, Evidence - A)

8. Persistently high serum ferritin and increased iron saturation, especially in the context of homozygote or heterozygote C282Y HFE mutations may warrant a liver biopsy. (Strength – 1, Evidence - B)

9. High serum titers of autoantibodies in association with other features suggestive of autoimmune liver disease (very high aminotransferases, high globulin) should prompt a more complete work-up for autoimmune liver disease. (Strength – 1, Evidence - B)

HEPATOLOGY, Vol. 55, No. 6, 2012

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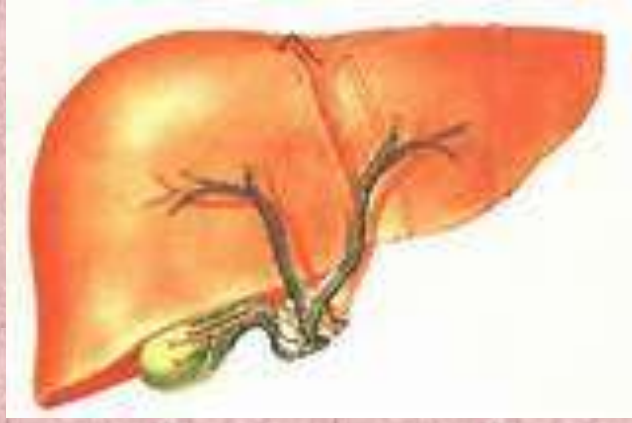
NAFLD Fibrosis Score: age, BMI, IFG or diabetes, AST, ALT, platelet count and albumin (low/medium or high risk of advanced fibrosis)

Diabetic Medicine 2015 Feb 12

NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

15. Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. (Strength – 1, Evidence - B)

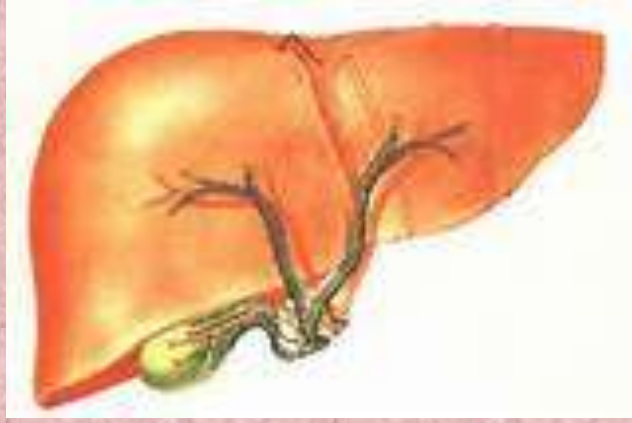
CASO CLINICO



- Ematochimici (consulenza gastronterologica): glicata 6,4%, glicemia 113 mg%, creatinina:1,29 mg%, AST 30, ALT 35, GGT 295, bilirubina tot 0,7, colesterolo tot 144, HDL 80, trigliceridi 48, Fe 79, transferrina 292, ferritina 151, HbsAg neg, antiHCV neg, ANA pos 1:320, AMA/ASMA/antiLKM, ANCA negativi

- VEROSIMILE NAFLD IN PAZIENTE IPERTESO, DIABETICO, OBESO

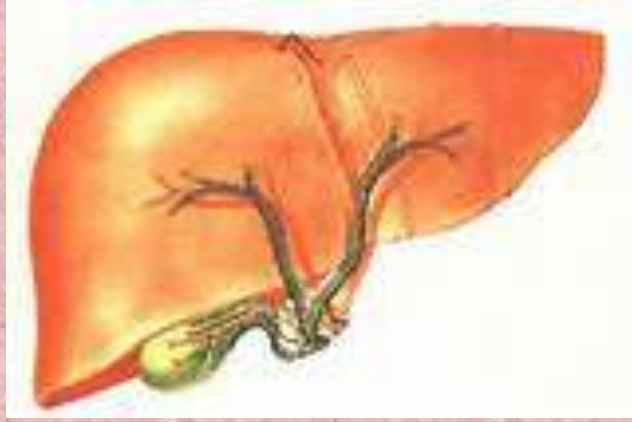
CASO CLINICO



- Ematochimici (consulenza gastronterologica): glicata 6,8%, glicemia 115 mg%, creatinina:1,21 mg%, AST 27, ALT 27, GGT 375, bilirubina tot 1, colesterolo tot 175, HDL 90, trigliceridi 56, ferritina 189, HbsAg neg, antiHCV neg, ANA pos 1:320. Dopo astensione assoluta da alcol per 30 gg: AST/ALT 36/52, GGT 350, bilirubina tot:1

- Fibroscan non eseguibile per spessore sottocutaneo > 2 cm

CASO CLINICO



PAZIENTE PRENOTATO PER BIOPSIA EPATICA PER DEFINIZIONE EZIOLOGICA DELL'EPATOPATIA (AI?/NASH?) E GRADING/STAGING

Review Article

Practical approach to non-alcoholic fatty liver disease in patients with diabetes

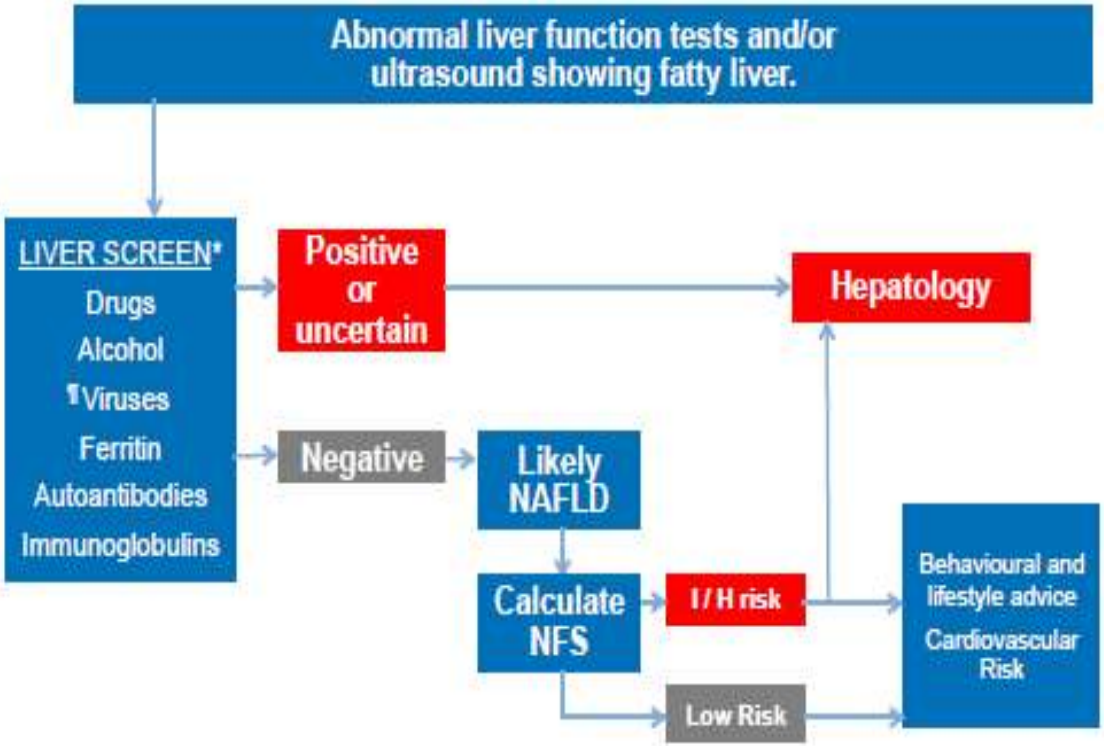
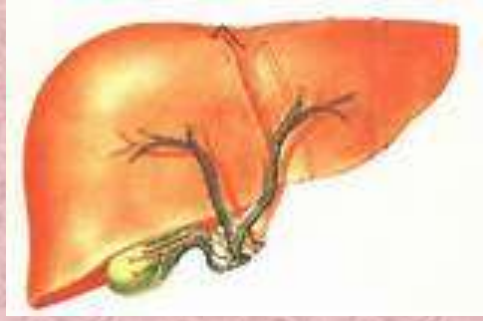


FIGURE 1 Diagnosis and risk stratification of patients with diabetes who are likely to have non-alcoholic fatty liver disease (NAFLD) based on the authors' opinions. *A complete liver screen would additionally include testing for α1-antitrypsin, caeruloplasmin and alphafetoprotein. ¶Chronic viral infection should be excluded by testing for hepatitis B virus surface antigen and antibodies against hepatitis C virus. NFS, NAFLD fibrosis score.

Diabetic Medicine 2015 Feb 12



World Journal of Gastroenterology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i45.16841

World J Gastroenterol 2014 December 7; 20(45): 16841-16857
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Focus on emerging drugs for the treatment of patients with non-alcoholic fatty liver disease

The therapeutic management targets of NAFLD are evolving; “treat the patient” and “treat the liver” should be both considered

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Recommendations

16. Weight loss generally reduces he
achieved either by hypocaloric
junction with increas
1, Evidence
weight
improve necroin-
1, Evidence - B)
alone in adults with NAFLD may
hepatic steatosis but its ability to improve other aspects of liver histology remains unknown. (Strength – 1, Evidence - B)

Effects of weight loss are inconstant due to the limited compliance of patients to diet and exercise

Hepatology 2009; 49 : 306-317

QUALITY OF DIET

There are limited randomized intervention study to generate evidence based dietary recommendations for NAFLD.

a "qualitative rather than quantitative" weight loss must be considered as the cornerstone for the treatment of hepa s

Patients with NAFLD may benefit - carbohydrate (40-45% of tot ased dietary MUFA and ructose corn syrup), ri gumes….

High levels of fructose in the diet may induce NAFLD and metabolic syndrome through different mechanism, such as bacterial translocation from gut to liver

World Journal of Gastroenterology, december 2014

Nutrients **2013**, *5*, 4093-4114; doi:10.3390/nu5104093

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

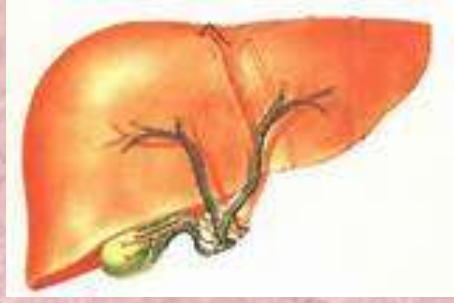
Recommendations

25. Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (but without established cirrhosis). (Strength – 1, Quality – A)

26. The type, safety and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis due to NAFLD are not established. (Strength – 1, Quality – B)

27. It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH (1B)

HEPATOLOGY, Vol. 55, No. 6, 2012



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.

55 patients with impaired glucose tolerance or type 2 diabetes and liver biopsy-confirmed nonalcoholic steatohepatitis to 6 months of treatment with a hypocaloric diet (a reduction of 500 kcal per day in relation to the calculated daily intake required to maintain body weight) plus pioglitazone (45 mg daily) or a hypocaloric diet plus placebo.

NEJM2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

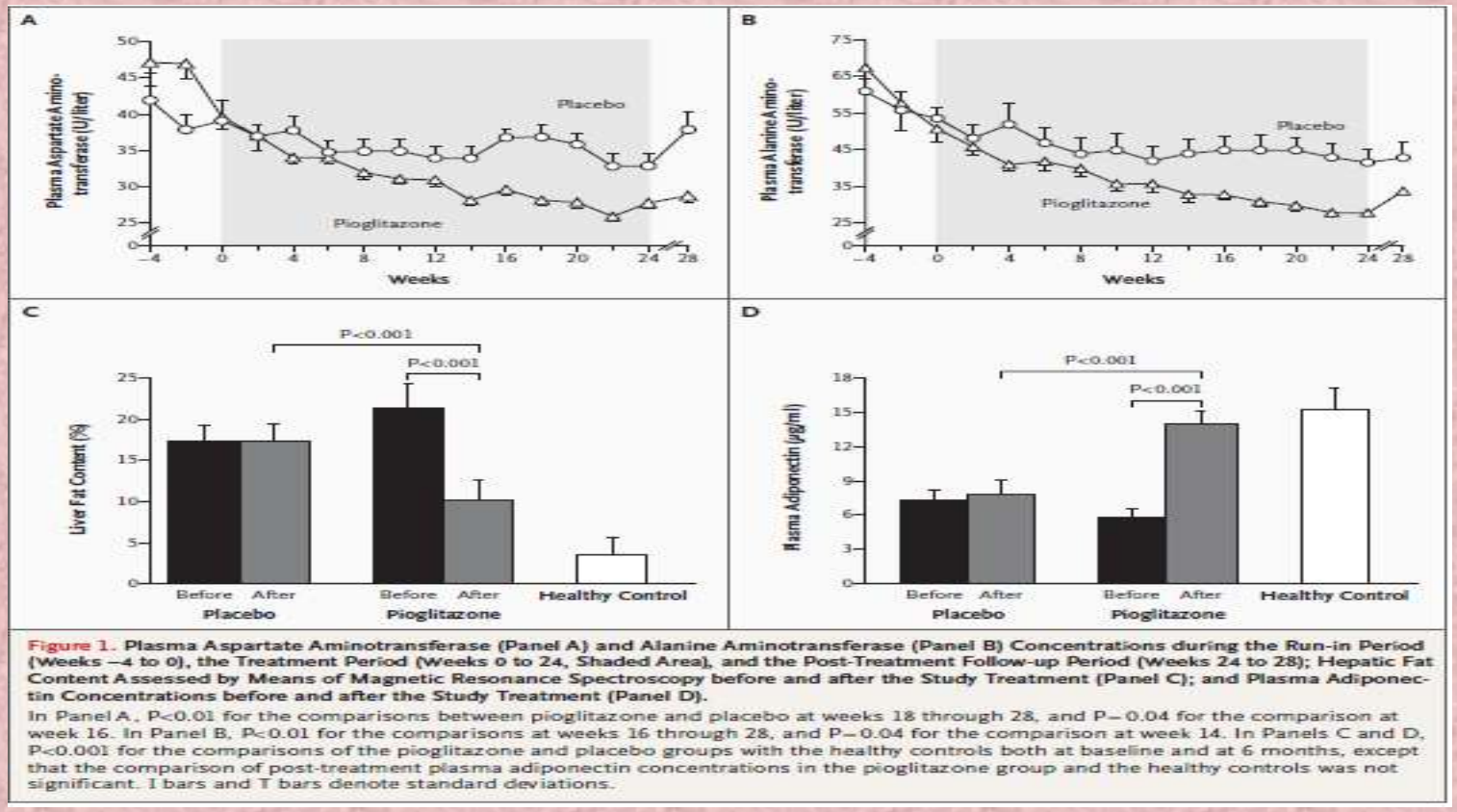


Figure 1. Plasma Aspartate Aminotransferase (Panel A) and Alanine Aminotransferase (Panel B) Concentrations during the Run-in Period (Weeks −4 to 0), the Treatment Period (Weeks 0 to 24, Shaded Area), and the Post-Treatment Follow-up Period (Weeks 24 to 28); Hepatic Fat Content Assessed by Means of Magnetic Resonance Spectroscopy before and after the Study Treatment (Panel C); and Plasma Adiponectin Concentrations before and after the Study Treatment (Panel D).

In Panel A, $P<0.01$ for the comparisons between pioglitazone and placebo at weeks 18 through 28, and $P=0.04$ for the comparison at week 16. In Panel B, $P<0.01$ for the comparisons at weeks 16 through 28, and $P=0.04$ for the comparison at week 14. In Panels C and D, $P<0.001$ for the comparisons of the pioglitazone and placebo groups with the healthy controls both at baseline and at 6 months, except that the comparison of post-treatment plasma adiponectin concentrations in the pioglitazone group and the healthy controls was not significant. I bars and T bars denote standard deviations.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

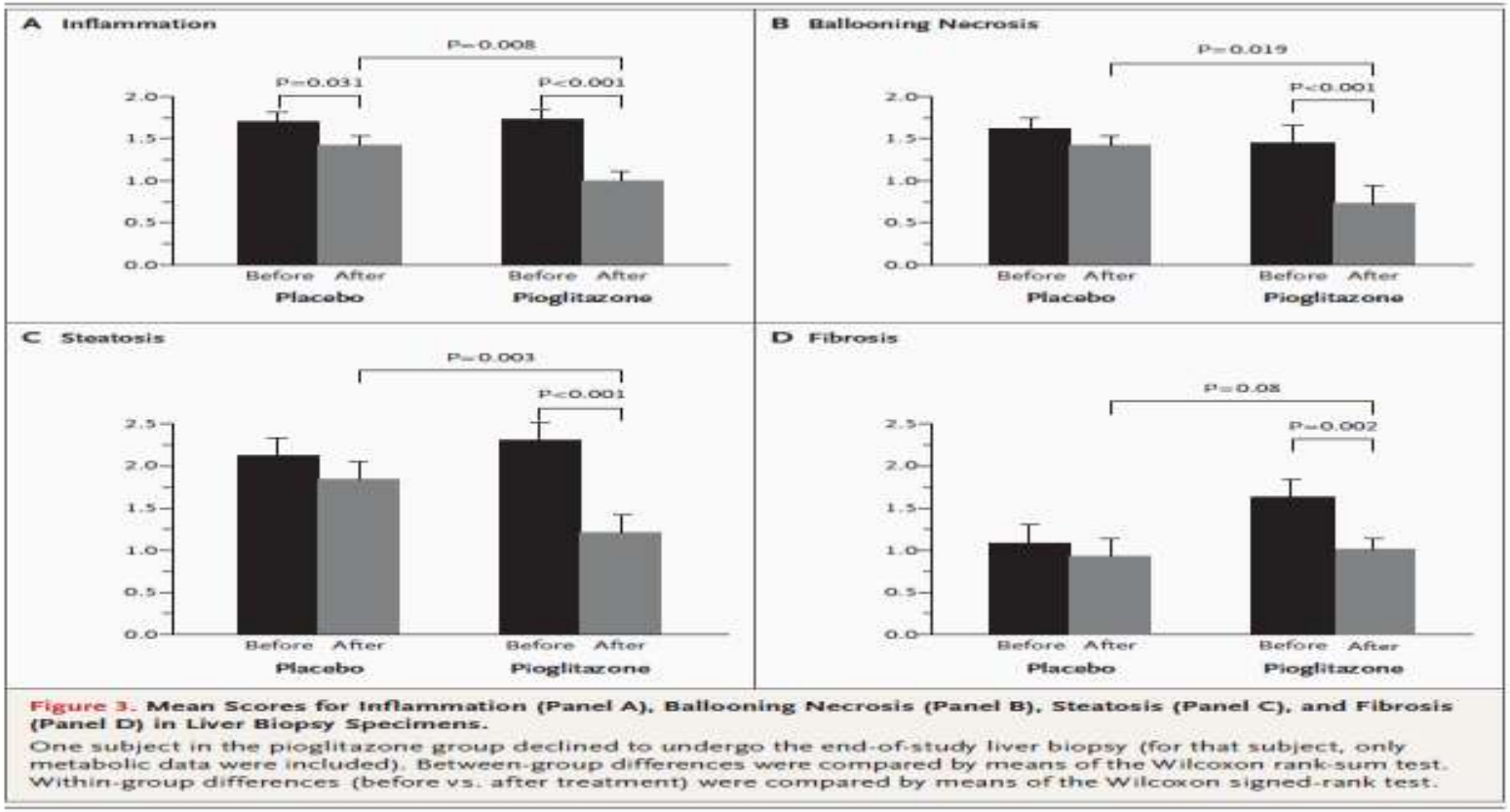


Figure 3. Mean Scores for Inflammation (Panel A), Ballooning Necrosis (Panel B), Steatosis (Panel C), and Fibrosis (Panel D) in Liver Biopsy Specimens.

One subject in the pioglitazone group declined to undergo the end-of-study liver biopsy (for that subject, only metabolic data were included). Between-group differences were compared by means of the Wilcoxon rank-sum test. Within-group differences (before vs. after treatment) were compared by means of the Wilcoxon signed-rank test.

The NEW ENGLAND JOURNAL of MEDICINE

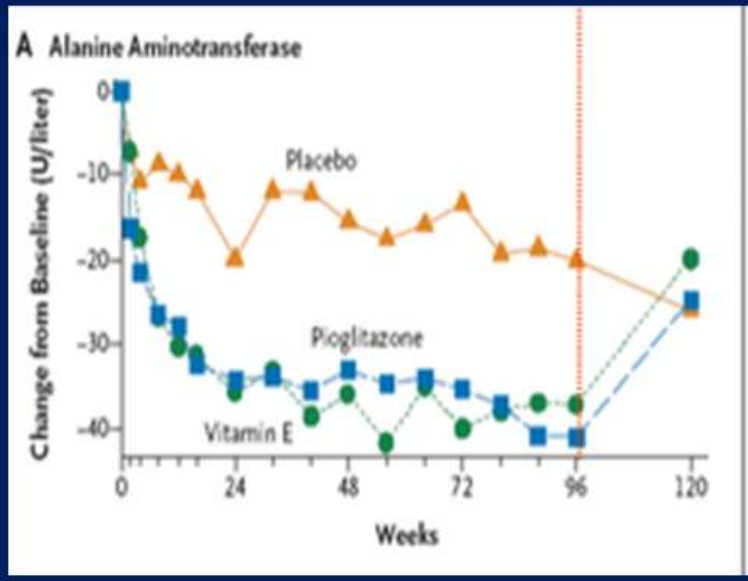
ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

247 adults with nonalcoholic steatohepatitis and without diabetes receive pioglitazone at a dose of 30 mg daily (80 subjects), vitamin E at a dose of 800 IU daily (84 subjects), or placebo (83 subjects), for 96 weeks

primary outcome was an improvement in histologic features of nonalcoholic steatohepatitis, as assessed with the use of a composite of standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis

NEJM 2010



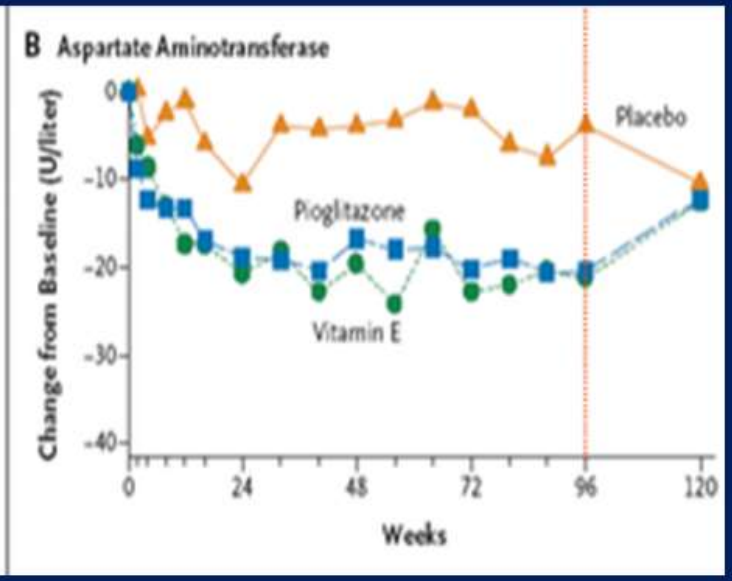


Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04

Sanyal et al NEJM 2010

Discontinuing TZD therapy has been shown to cause an immediate NASH recurrence. Long-term use is required for the achievement of treatment results; however, the duration can cause medical complications, such as edema, congestive heart failure, osteoporosis and weight gain

World Journal of Gastroenterology 2014 Dec 7;20(45):16841-57

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Recommendation

20. Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established. (Strength – 1, Evidence - B)

HEPATOLOGY, Vol. 55, No. 6, 2012

METFORMINA

Metformin improves IR by decreasing hepatic glucose production and increasing skeletal muscle glucose uptake;

This drug also reduces the hepatic expression of TNF-α,a mediator of hepatic insulin resistance and necro-inflammation;

Increases FFA oxidation and suppresses lipogenesis through AMP-kinase activation

World Journal of Gastroenterology 2014 Dec 7;20(45):16841-57

Table 4. Selected Studies of Metformin in Patients with NAFLD

Author (reference)	N	Design	Comparator	Population	Duration	Liver Enzymes	Histology
Marchesini et al.[142]	14	Open label Single arm	None	Adults Mostly nondiabetic	4 mo	Improved	Not evaluated
Nair et al.[143]	15	Open label Single arm	None	Nondiabetics	12 mo	Improved	Improved inflammation
Uygun et al.[144]	36	Open label	Calorie-restricted diet	Nondiabetics	6 mo	Improved	Improved inflammation
Bugianesi et al.[145]	55	Randomized clinical trial	Calorie restricted diet	Non-diabetics	12 mo	Improved	Improved steatosis, inflammation and fibrosis
Schwimmer et al.[146]	10	Open label Single arm	None	Nondiabetics	6 mo	Improved	Not evaluated
Loomba et al.[147]	14	Open label Single arm	None	Nondiabetics	48 wks	Improved	Improved steatosis and inflammation
Nobili et al.[148]	57	Open label	Antioxidant	Nondiabetics	24 months	No difference	No difference

Vuppalanchi V., Hepatology 2009; 49: 306-317

Effect of Vitamin E or Metformin for Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents

The TONIC Randomized Controlled Trial

To determine whether children with NAFLD would improve from therapeutic intervention with vitamin E or metformin

Daily dosing of 800 IU of vitamin E (58 patients), 1000 mg of metformin (57 patients), or placebo (58 patients) for 96 weeks

The primary outcome was sustained reduction in alanine aminotransferase (ALT) defined as 50% or less of the baseline level or 40 U/L or less at visits every 12 weeks from 48 to 96 weeks of treatment. Improvements in histological features of NAFLD and resolution of NASH were secondary outcome measures.

JAMA,2011

Table 2. Primary Outcome: Sustained Reduction in ALT Level by Treatment Group

	Vitamin E (n = 58)	Metformin (n = 57)		P Value[a] Vitamin E vs Placebo	P Value[a] Metformin vs Placebo
Sustained reduction in ALT level, No. (%) [95% CI][b]	15 (26) [15 to 39]	9 (16) [7 to 28]		.26	.83
Relative efficacy vs placebo, % (95% CI)[c]	50 (–36 to 206)	–9 (–149 to 109)			
Change in ALT level from baseline, mean (95% CI), U/L[d]					
Week 24	–49.2 (–64.4 to –33.9)	–3.0 (–21.1			.09
Week 48	–44.5 (–60.3 to –28.7)	–11.7 (–45			.52
Week 72	–44.2 (–65.9 to –22.5)	–20.5 (		.29	.51
Week 96	–48.3 (–66.8 to –29.8)	–41		.07	.40

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval.
[a] Based on χ^2 test for binary outcomes or analysis-of-covariance model regressing change from … outcome for continuous outcomes.
[b] Sustained reduction defined as ALT ≤40 U/L or ≤0.5 × baseline ALT level at 48-, 60-, 72… …uted as no sustained reduction if data were missing either at week 96 or at all 4 visits from week 48 to week 84; numbers im… …d placebo groups, respectively.
[c] Relative efficacy vs placebo = (1 – relative risk) × 100.
[d] Number of patients with complete data was similar across treatment groups at ea…

Table 3. Change From Baseline to End of Treatment …

			Placebo (n = 47)	P Value[a] Vitamin E vs Placebo	P Value[a] Metformin vs Placebo
Fibrosis score					
No. (%) improved [95% CI]		…4) [30 to 59]	19 (40) [26 to 56]	.71	.72
Mean change (95% CI)		…4 (–0.7 to –0.0)	–0.2 (–0.6 to 0.1)	.48	.60
Steatosis score					
No. (%) improved [95% CI]		26 (52) [37 to 66]	19 (40) [26 to 56]	.18	.25
Mean change (95% CI)		–0.6 (–0.9 to –0.2)	–0.4 (–0.8 to –0.1)	.24	.50
Lobular inflammation score					
No. (%) improved [95% C…	…59]	23 (46) [32 to 61]	20 (43) [28 to 59]	.89	.73
Mean change (95% C…	…–0.2)	–0.3 (–0.5 to –0.0)	–0.3 (–0.6 to –0.1)	.14	.97
Ballooning degeneration					
No. (%) improved [95…	…4) [30 to 59]	22 (44) [30 to 59]	10 (21) [11 to 36]	.02	.02
Mean change (95% CI)	…(–0.8 to –0.3)	–0.3 (–0.6 to –0.0)	0.1 (–0.2 to 0.3)	.006	.04
Change in NAFLD activity score, …	…1.8 (–2.4 to –1.2)	–1.1 (–1.7 to –0.5)	–0.7 (–1.3 to –0.2)	.02	.25
Resolution of NASH, No. (%) [95% C…	25 (58) [42 to 73]	16 (41) [26 to 58]	11 (28) [15 to 45]	.006	.23

Abbreviations: CI, confidence interval; NAFL… …tty liver disease; NASH, nonalcoholic steatohepatitis.
[a] *P* values derived from either χ^2 test for binary … analysis-of-covariance model regressing change from baseline to 96 weeks on treatment group and baseline value of the outcome for continuous outcomes.
[b] Defined as number of patients with no NASH at wee…6 among patients with borderline or definite NASH at baseline. Excludes 7, 11, and 8 patients with no NASH at baseline in vitamin E, metformin, and placebo groups, respectively.

no significant reduction in transaminases compared with placebo in the metformin group, and no significant change in histology, except for hepatocellular ballooning

JAMA,2011

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Recommendation

19. Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. (Strength – 1, Evidence - A)

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

21. Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength - 1, Quality - B)

22. Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (Strength - 1, Quality - C)

24. It is premature to recommend omega-3 fatty acids for the specific treatment of NAFLD or NASH but they may be considered as the first line agents to treat hypertriglyceridemia in patients with NAFLD. (Strength – 1, Quality – B)

HEPATOLOGY, Vol. 55, No. 6, 2012

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Other anti-diabetic medication?

HEPATOLOGY, Vol. 55, No. 6, 2012

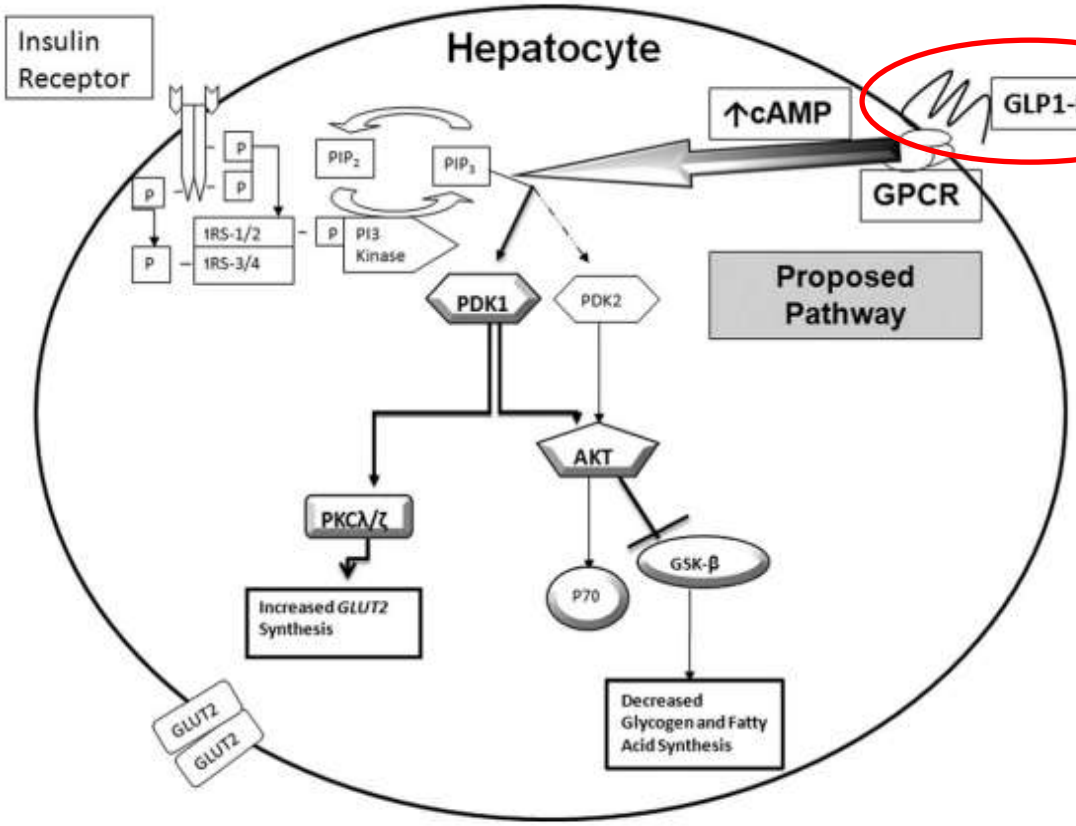


Fig. 6. Proposed GLP-1R signal transduction scheme. In our previous work, we demonstrated that GLP-1 or exendin-4 increased cyclic adenosine monophosphate (cAMP) production. Here we propose that the GLP-1 action shares key downstream components of the insulin signaling pathway, including PKC-ζ, which has been shown to be a key factor in NAFLD.

Gupta NA et al., Hepatology. 2010

➢Si ipotizza che vi possa essere da parte dei GLP-1 analoghi un effetto diretto a livello epatocitario, mediato da un recettore specifico presente a livello del fegato.

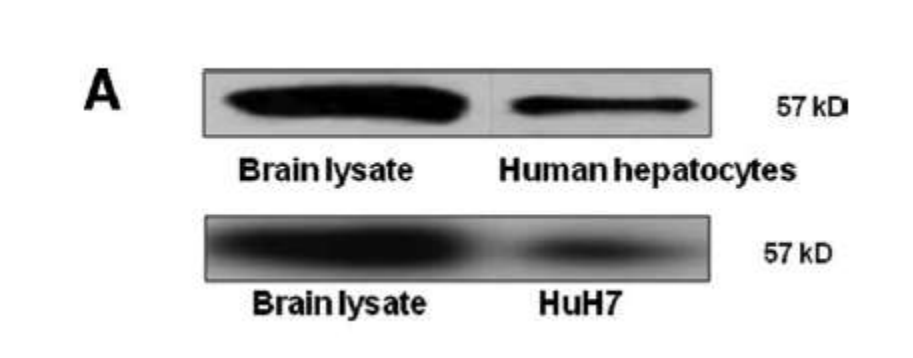
Samson SL et al. Journal of Diabetes and its complications 2013, 27, 4: 401-406.

Gupta NA, Hepatology 2010; 51:1584-1592.

Glucagon-Like Peptide-1 Receptor Is Present on Human Hepatocytes and Has a Direct Role in Decreasing Hepatic Steatosis *In Vitro* by Modulating Elements of the Insulin Signaling Pathway

Nitika Arora Gupta,[1,2*] Jamie Mells,[3*] Richard M. Dunham,[4] Arash Grakoui,[4] Jeffrey Handy,[5] Neeraj Kumar Saxena,[5] and Frank A. Anania[5]

Hepatology 2010; 51:1584-1592



BMJ Open

Liraglutide efficacy and action in non-alcoholic steatohepatitis (LEAN): study protocol for a phase II multicentre, double-blinded, randomised, controlled trial

Matthew J Armstrong,[1,2] Darren Barton,[3] Piers Gaunt,[3] Diana Hull,[1] Kathy Guo,[1] Deborah Stocken,[4] Stephen C L Gough,[5] Jeremy W Tomlinson,[6] Rachel M Brown,[7] Stefan G Hübscher,[7,8] Philip N Newsome,[1,2] on behalf of the LEAN trial team

Dipeptidyl peptidase-4: A key player in chronic liver disease

Minoru Itou, Takumi Kawaguchi, Eitaro Taniguchi, Michio Sata

Il knock-out del gene della DPP-4 causa direttamente l'attivazione del PPARα e l'inattivazione dello SREBP-1, con conseguente aumento della ossidazione lipidica e riduzione della lipogenesi e riduzione della steatosi epatica indotta da una dieta ricca in grassi. (Conarello SL et al., *Proc Natl Acad Sci USA* 2003; 100: 6825-6830)

Itou M.et al. World J Gastroenterol 2013 April 21; 19(15): 2298-2306

NAFLD E DDP4

✓L'espressione del mRNA del DPP-4 epatico è significativamente più alto nei pazienti con NAFLD rispetto ai soggetti normali.

Miyazaki M et al. *Mol Med Rep* 2012;5: 729-733

✓L'attività della DPP-4 sierica e l'espressione epatica della DPP-4 sono correlate con la steatosi epatica e con il grading della NAFLD

Balaban YH et al. Ann Hepatol 2007; 6: 242-250.

✓Recenti studi hanno dimostrato la capacità degli inibitori della DPP-4 di migliorare la steatosi epatica sia nell'animale che nell'uomo

Shirakawa J. et al. Diabetes 2011; 60: 1246-1257

Yilmaz T. et al. Acta Gastroenterol Belg 2012; 75:240-244

✓E' stato pubblicato un caso di NAFLD refrattaria alle terapie, trattata con successo con sitagliptin.

Itou M.et al. Case Rep Gastroenterol 2012; 6:538-544


INSULINA

Diabetes & Metabolism

Goh et al., J Diabetes Metab 2014, 5:8
http://dx.doi.org/10.4172/2155-6156.1000410

Research Article Open Access

Diabetes Mellitus, Insulin, Sulfonylurea and Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

Clinical information including demographics, medical history, medication history, biochemical and histologic variables were ascertained in 459 patients with biopsy proven non-alcoholic fatty liver disease. We compared characteristics of patients with and without diabetes and explored potential associations between classes of drugs as risk factors and advanced fibrosis among the diabetic patients with NAFLD

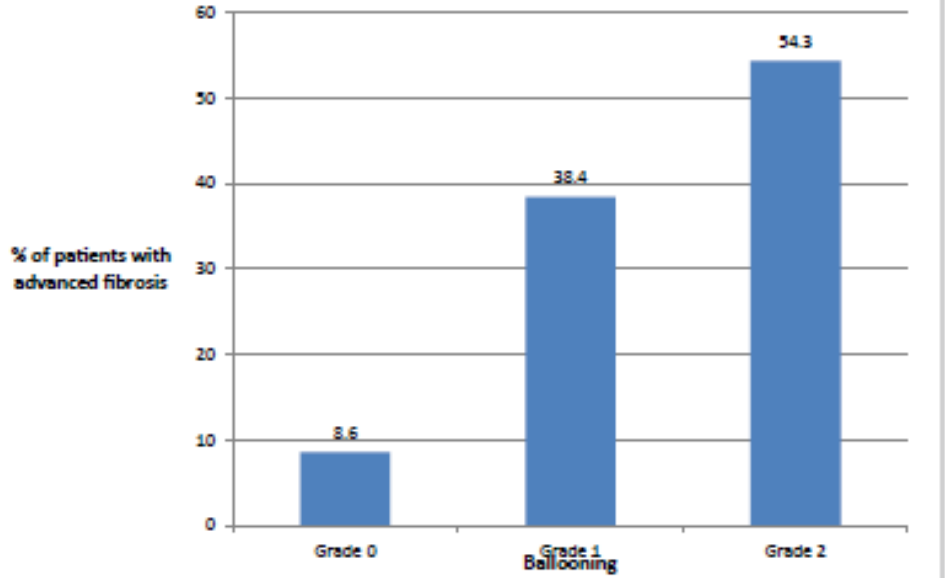


Figure 1: Relationship of grade of ballooning to advanced fibrosis in NAFLD patients with DM.

Multivariate analysis of advanced fibrosis risk factors. Use of insulin and sulfonylurea were positively associated with advanced fibrosis. In contrast, the use of statins was negatively associated with advanced fibrosis.

Variable	DM cohort		Cross validation 80:20.	
	OR; 95% CI	P value	OR; 95% CI	P value
Age	1.09; 1.04-1.15	0.000	1.12; 1.06-1.19	0.000
Ballooning	5.59; 2.69-11.61	0.000	7.01; 3.01-16.33	0.000
Use of Insulin	4.95; 1.65-14.88	0.004	4.64; 1.35-15.95	0.015
Use of Sulfonylurea	5.07; 1.87-13.75	0.001	4.63; 1.43-15.00	0.011
Use of Statins	0.31; 0.12-0.78	0.013	0.30; 0.10-0.86	0.025

Covariates included were age, BMI, gender, presence of hypertension, lipids, histology, use of insulin, metformin, sulfonylurea, statin and ACE-I/ARB.

OR: Odds ratio, CI: Confidence interval.

Table 4: Independent risk factors of advanced fibrosis in DM subjects.

Pharmacokinetic and toxicological considerations for the treatment of diabetes in patients with liver disease

Table 4. Clinical practice recommendations regarding the use of glucose-lowering agents in diabetic patients with various degrees of hepatic impairment (HI).

Medications	Mild HI	Moderate HI	Severe HI	Feared adverse event
Biguanides				
Metformin	Yes*	Caution	No use	Lactic acidosis[§]
Sulfonylureas				
Glibenclamide (glyburide), glimepiride, glipizide, gliclazide, gliquidone	Yes	Caution	No use	Hypoglycemia
Glinides				
Repaglinide, nateglinide	Yes	Caution	No use	Hypoglycemia
Alpha-glucosidase inhibitors				
Acarbose, miglitol, voglibose	Yes	Probably yes	Probably yes	Hyperamonemia
Thiazolidinediones				
Pioglitazone, rosiglitazone	Yes[†]	Caution (check liver enzymes)	No use	Hepatotoxicity (?)
DPP-4 inhibitors				
Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Yes	Probably yes	Caution	Unknown (but no clinical experience
SGLT2 inhibitors				
Dapagliflozin, canagliflozin, empagliflozin	Yes	Caution	No use	Unknown (but no clinical experience
GLP-1 receptor agonists				
Exenatide, liraglutide, lixisenatide	Yes	Probably yes	Caution or no use	Unknown (but no clinical experience
Insulin and insulin analogs	Yes	Yes	Yes with caution	Hypoglycemia

Insulin treatment is frequently required in patients with diabetes and liver disease. Insulin requirements, however, may vary.

liver disease:

decompensated requirement may be decreased due to reduced capacity for gluconeogenesis and reduced hepatic breakdown of insulin

patients with impaired hepatic function may have an increased need for insulin due to insulin resistance

K. G. Tolman, Diabetes Care, 2007

In patients with hepatic encephalopathy who require high-carbohydrate diets, resulting in postprandial hyperglycemia, rapid-acting insulin analogs may be particularly useful

K. G. Tolman, Diabetes Care, 2007

PREVENZIONE

Table 3: The level of available evidence and grade of recommendations for treatment of NAFLD.

Intervention	Outcome(s)	Level of Evidence	Recommendation Grade
Weight reduction- exercise	Histology-biochemistry	1	A
Vitamin E	Biochemistry	2	B*
Metformin (In diabetic patients)	Biochemistry	2	B
Pioglitazone	Histology-biochemistry	1	A
Probucol	Biochemistry	2	B
Betaine	Histology-biochemistry	4	C
Ursodeoxycholic acid	Biochemistry	2	B**
Probiotics	Biochemistry	3	C
Statins (In metabolic syndrome)	Imaging-biochemistry	1	A***
Angiotensin II receptor blockers (in metabolic syndrome)	Histology-biochemistry	3	C****
Orlistat (in obese patients)	Histology-biochemistry	2	B*****

* One systematic review of poor quality RCTs did not provide evidence on the pros or cons of antioxidant supplements, including vitamin E in NAFLD or NASH.[56]

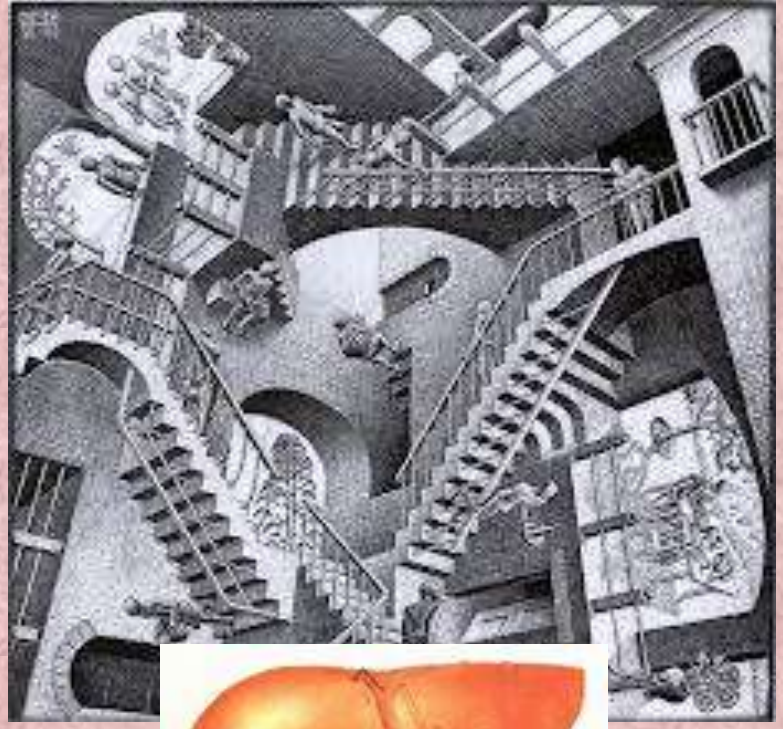
** In a systematic review, no significant differences were found regarding mortality or improvement in liver function tests observed after treatment with UDCA.[52]

***There was no benefit in patients without metabolic syndrome and in the histological features of the NASH with statins.[63]

**** Histological improvement was seen only with telmisartan, perhaps because of its specific PPAR-gamma ligand effect.[64]

***** Weight reduction was more important than orlistat use, when the beneficial effects of orlistat were studied.[10]

Middle East Journal of Digestive Diseases/ Vol.1/ No.2/ September 2009

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GRAZIE PER LA VOSTRA ATTENZIONE!!!!