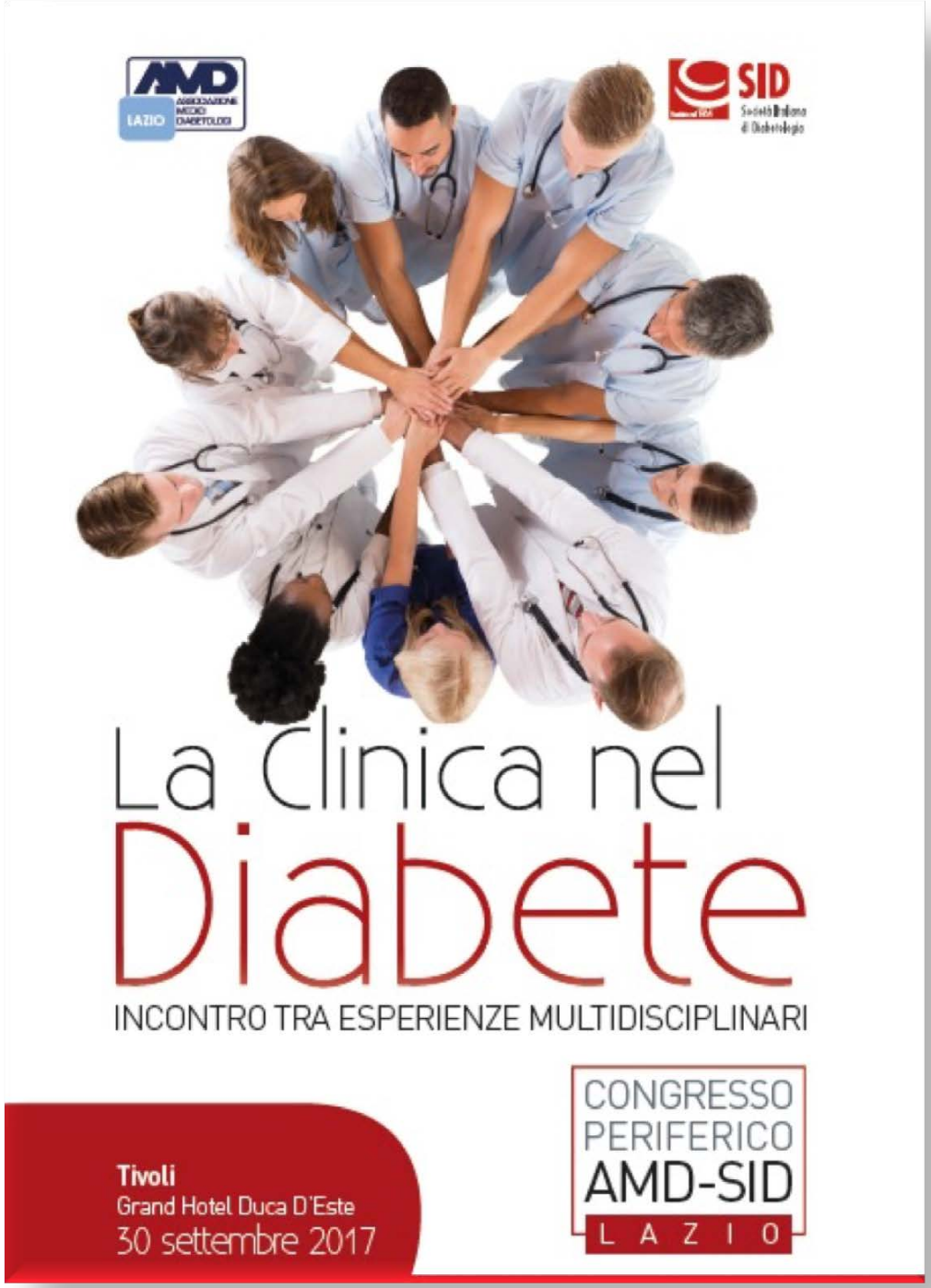


Percorso Fegato e Diabete

Caso clinico:

Terapia antidiabetica in corso di epatopatia cronica

Daniela Bracaglia
Danila Capoccia

CONGRESSO PERIFERICO AMD-SID

LA CLINICA DEL DIABETE INCONTRO TRA ESPERIENZE MULTIDISCIPLINARI
Tivoli, 30 settembre 2017

- le dr./sse BRACAGLIA e CAPOCCIA dichiarano di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

- E.M. è un idraulico di 60 anni
- Anamnesi familiare
  - padre e fratello affetti da ipertensione e diabete tipo 2
  - fratello con epatopatia (non ben identificata)
- Anamnesi fisiologica:
  - ex fumatore
  - segue un'alimentazione ricca in carboidrati e grassi animali, alcool max 20 gr/die
  - stile di vita sedentario
- Anamnesi patologica remota:
  - ipertensione dal 1997 in terapia con ace inibitore
  - diabete tipo 2 dal 2011 non in trattamento
  - pregressa asportazione polipi colon con displasia basso grado
  - *dal 2010 riscontro di iperGGT ad andamento oscillante e lieve movimento transaminasi*

- Esame obiettivo
  - peso: 92 kg, h: 170 cm, cv: 109 cm, BMI: 32 kg/m^2
  - PA: 150/80 mmhg
  - EOC e EOT: ndr; EOA: lieve epatomegalia
- Esami ematici disponibili …
  - FPG: 140 mg/dl
  - HbA_{1c}: 7% (53 mmol/mol)
  - Creatinina:1,2 mg/dl; GFR secondo EPI-CKD: 65 ml/min/1.73m^2
  - AST: 36 U/I (vn<40 U/I); ALT: 40 U/I (v.n.<41U/I); GGT: 210 U7l (v.n.: 55 U/l); Col TOT: 210 mg/dl, TGL: 187 mg/dl,HDL: 45; LDL (calcolato): 128 mg/dl.
  - Ecografia addome: epatomegalia steatosica, margini arrotondati, non lesioni focali, non formazioni litiasiche della colecisti, coledoco nella norma

Perché è necessario valutare il quadro epatico nel paziente diabetico?

- Nel *Verona Study* (7148 pz seguiti per un follow up medio di 5 anni) il rischio di morte per cause epatiche era risultato significativamente più elevato rispetto a quello della popolazione generale (De Marco R, Diabetes Care 1999; 22: 756-61)
- In uno *studio canadese* la presenza di diabete neodiagnosticato si associava ad un rischio doppio di sviluppare forme di epatopatia severa (cirrosi, scompenso epatico, necessità di trapianto epatico) rispetto alla popolazione non diabetica. (Porepa L, CMAJ 2010 182: E526-E531)
- Un *recente studio italiano*, condotto su diabetici noti, ha confermato che i pz diabetici hanno una probabilità di morte per patologia epatica aumentata di circa 2,5 volte rispetto alla popolazione generale. (Zoppini G, Am J Gastr, 2014; 109: 1020-1025)
- Un altro *studio retrospettivo* su diabetici tipo 2, seguiti per un follow up medio di 11 anni, ha dimostrato che i pz con NAFLD avevano un rischio di mortalità totale che era almeno doppio rispetto a quelli senza NAFLD. (Adams LA, AM J Gastr, 2010; 105: 1567-1573)

Spectrum of liver disease in diabetes

- Abnormal liver enzymes
- Cirrhosis
- Hepatocellular carcinoma
- Acute liver failure
- Hepatitis C
- NAFLD

KG Tolman, Diabetes Care, 2007

Quali esami chiedere in questo paziente per definire il quadro epatico?

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

Diagnosi di NAFLD

Per porre diagnosi di NAFLD è necessario:

a) che vi sia evidenza di un quadro di steatosi epatica (tramite tecniche di imaging o istologia);
b) che siano escluse altre cause note di epatopatia cronica

Dal punto di vista istopatologico, la NAFLD comprende uno spettro di condizioni che includono la steatosi semplice, la steato-epatite non alcolica (NASH) caratterizzata da steatosi e necroinfiammazione e la cirrosi che può talora evolvere verso epatocarcinoma

Chalasani N, Hepatology 2012; 55: 2005-23

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)
- **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)

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

Chalasani N, Hepatology 2012; 55: 2005-23

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

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)

Chalasani N, Hepatology 2012; 55: 2005-23

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

Recommendations

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

14. The presence of metabolic syndrome and the 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)

Chalasani N, Hepatology 2012; 55: 2005-23

NAFLD Fibrosis Score vs FIB-4 score

NAFLD Fibrosis Score

Parametri
Età (anni)
AST
ALT
Piastrine (x 10^9)
BMI
Albumina, gr/L
Glicemia aumentata a digiuno / diabete ?

FIB-4 score

NAFLD Cutoff Value[1]	Stadio
< -1.455	F0-F2
-1.455 to 0.676	Indeterminato
> 0.676	F3-F4

FIB-4 Cutoff Value[2]	Stadio
< 1.45	F0-F2
1.45 to 3.25	Indeterminato
> 3.25	F3-F4

1. Angulo P, et al. Hepatology. 2007;45:846-854.
2. Sterling RK, et al. Hepatology. 2006;43:1317-1325.

Stadiazione non invasiva della fibrosi epatica

Markers Sierologici

- ✓ Simple
  - ✓ AST/ALT ratio
  - ✓ FIB-4 index
  - ✓ APRI (AST to-platelet ratio index)
  - ✓ NAFLD fibrosis score
- ❖ Complex
  - ❖ NASH *FibroSURE*
  - ❖ ELF (Enhanced Liver Fibrosis)
  - ❖ HA (Hyaluronic Acid)

Tecniche di Imaging

- ➢ Elastography
  - ➢ VCTE (Vibration-Controlled Transient Elastography) *FibroScan*
  - ➢ MR elastography
  - ➢ ARFI (Acoustic Radiation Force Impulse)
  - ➢ SSI (Supersonic Shear Imaging)

Caso clinico

- Esami ematici richiesti
  - FPG: 145 mg/dl
  - HbA_{1c}: 7.6% (53 mmol/mol)
  - Creatinina: 1,19 mg/dl
  - AST: 30 U/I (vn<40 U/I)
  - ALT: 59 U/I (v.n.<41U/I)
  - GGT: 295 U7l (v.n.: 55 U/l)
  - bilirubina totale: 0,7 gr/dl
  - ferro: 79 mcg/dl (v.n. 50-150 mcg/dl)
  - ferritina: 151μ/l (v.n.: 20-300 μ/l)
  - transferrina: 292 mg/dl (v.n.: 215-365 mg/dl)
  - albuminemia: 3,9 gr/dl
  - emocromo: nella norma (piastrine: $150x10^9$/l)
  - Anti-HCV: negativo; HBsAG: negativo; anti HBsAg: negativo; anti HBcAg: negativo
  - ANA pos1:320; AMA/ASMA/antiLKM, ANCA negativi

Verosimile NAFLD in paziente iperteso, diabetico, obeso

Domanda: Quale è la prevalenza della NAFLD nella popolazione generale e nel diabete tipo 2?

a. 20 e 50%

b. 10 e 80%

c. 30 e 70%

d. 5 e 90%

Domanda: Quale è la prevalenza della NAFLD nella popolazione generale e nel diabete tipo 2?

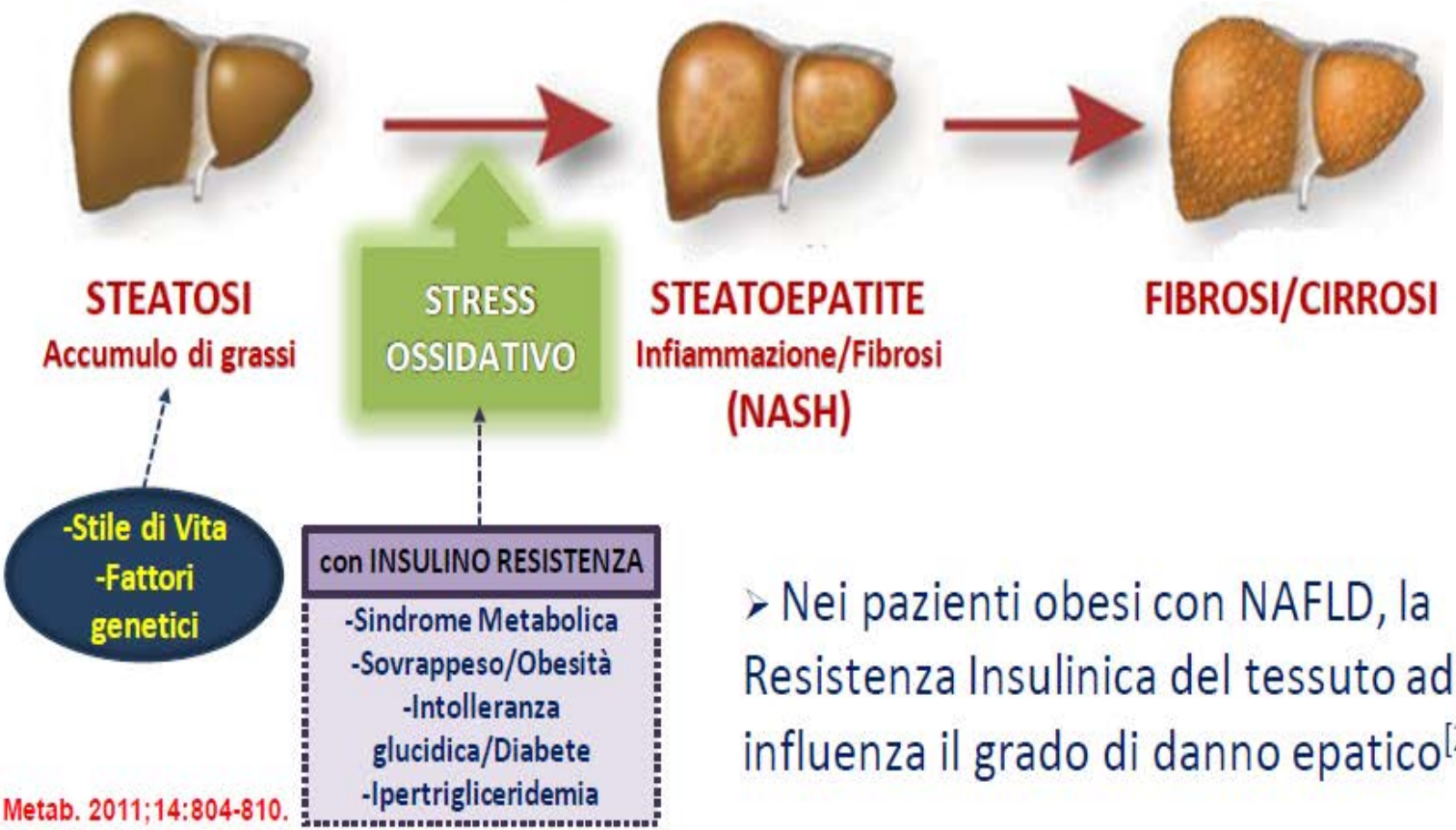
c. 30 e 70%

- La NAFLD è la più comune causa di epatopatia cronica nei paesi occidentali (30% della popolazione generale) si correla a obesità e insulino-resistenza.
- La prevalenza della NAFLD nel diabete tipo 2 si attesta sul 60-70% e può arrivare a valori più elevati in base al grado di obesità (90% degli obesi che si sottopongono a chirurgia bariatrica.
- I diabetici tipo 2 non solo hanno una maggiore probabilità di manifestare la NAFLD, ma anche di avere le forme istologiche più severe quali NASH (20%) che a sua volta determina l'evoluzione in cirrosi in una percentuale variabile.
- Inoltre la NAFLD nei soggetti diabetici si associa ad aumentato rischio cardiovascolare e aumentato rischio di insufficienza renale

Progressione della NAFLD

- Nella NAFLD, l' aumento del flusso di Acidi Grassi al fegato ed ai mitocondri produce uno stress ossidativo ed un danno epatico[1]

  - Nonostante l' aumentata ossidazione da parte dei mitocondri epatici, il fegato è incapace di adattarsi al cronico sovraccarico dei substrati



- Nei pazienti obesi con NAFLD, la Resistenza Insulinica del tessuto adiposo influenza il grado di danno epatico[2]

1.Sunny NE, et al. Cell Metab. 2011;14:804-810.
2. Lomonaco R, et al. Hepatology. 2012;55:1389-1397.

Caso clinico

- Esami ematici ripetuti dopo 30 gg di astensione assoluta da alcool:
  - FPG: 138 mg/dl
  - HbA_{1c}: 7.5% (53 mmol/mol)
  - Creatinina: 1,21 mg/dl
  - AST: 36 U/I (vn<40 U/I)
  - ALT: 52 U/I (v.n.<41U/I)
  - GGT: 250 U/l (v.n.: 55 U/l)
  - Colesterolo totale: 208 mg/dl
  - HDL: 46 mg/dl
  - TGL: 150 mg/dl

Fibroscan non eseguibile per spessore sottocutaneo >2 cm.

NAFLD Fibrosis score: 2, FIB-4 score: 2,03

Domanda: La presenza di ipertransaminasemia nel diabete è imputabile a:

a. infezione virale, abuso di alcol NAFLD, a seconda del profilo biochimico e laboratoristico

b. sempre da mettere in rapporto all'obesità

c. sempre riferibile ad un consumo di alcol superiore a 30 gr/die

d. da riferire all'uso di statine

Domanda: La presenza di ipertransaminasemia nel diabete è imputabile a:

a. infezione virale, abuso di alcol
NAFLD, a seconda del profilo
biochimico e laboratoristico

Quale trattamento consigliare al nostro paziente?

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
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

At present there are three approaches to NAFLD treatment: life style changes (diet and/or physical exercise), medications and surgical interventions

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

Recommendations

16. Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. (Strength – 1, Evidence - A)

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

Hepatology 2009; 49:306-317

18. Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown. (Strength – 1, Evidence - B)

Chalasani N, Hepatology 2012; 55: 2005-23

Quality of diet

- There are limited randomized intervention on study to genrate evidence based dietary recommendations for NAFLD
- a "qualitative rather than quantitative" weight loss must be considered as the cornerstone for the treatment of hepatic disease
- Pati
carb
incr
and
those found in whole grains, legumes, fruits and vegetables

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

World J of Gastr,december 2014

Conlon BA, Nutrients 2013; 5: 4093-4114

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

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)

Chalasani N, Hepatology 2012; 55: 2005-23

Domanda: La terapia di elezione per la NAFLD, oltre allo stile di vita, si basa sull'uso di:

a. insulinosensibilizzanti

b. astensione assoluta dall'alcool

c. uso di sostanze antiossidanti

d. Uso di statine e/o fibrati

Domanda: La terapia di elezione per la NAFLD, oltre allo stile di vita, si basa sull'uso di:

a. insulinosensibilizzanti

metformina

- La metformina migliora l'insulino resistenza diminuendo la produzione epatica di glucosio e aumentando l'uptake di glucosio da parte del muscolo
- Inoltre riduce l'espressione epatica del TNFa, responsabile dell'insulino resistenza epatica e dell'infiammazione
- Aumenta l'ossidazione degli acidi grassi e sopprime la lipogenesi attraverso l'attivazione dell'AMPchinasi

Federico A., W J Gastr 2014 Dec 7; 20 (45):16841-57

Meta- Analysis of Randomized Controlled Trials of Pharmacologic Agents in non –alcoholic Steatohepatitis

Conclusion:…. in patient with NASH histological parameters, including ballooning, fibrosis, staetosis and NAFLD activity score (NAS) did not significantly change with metformin therapy.

Biochemical parameters including fasting blood sugar, HOMA-IR, total cholesterol, ALT, body weight and BMI, all significantly improved with metformin therapy as compared to the control group

Said A, Annals of Hepatology 2017; 16 (4): 538-47

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

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)

Chalasani N, Hepatology 2012; 55: 2005-23

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

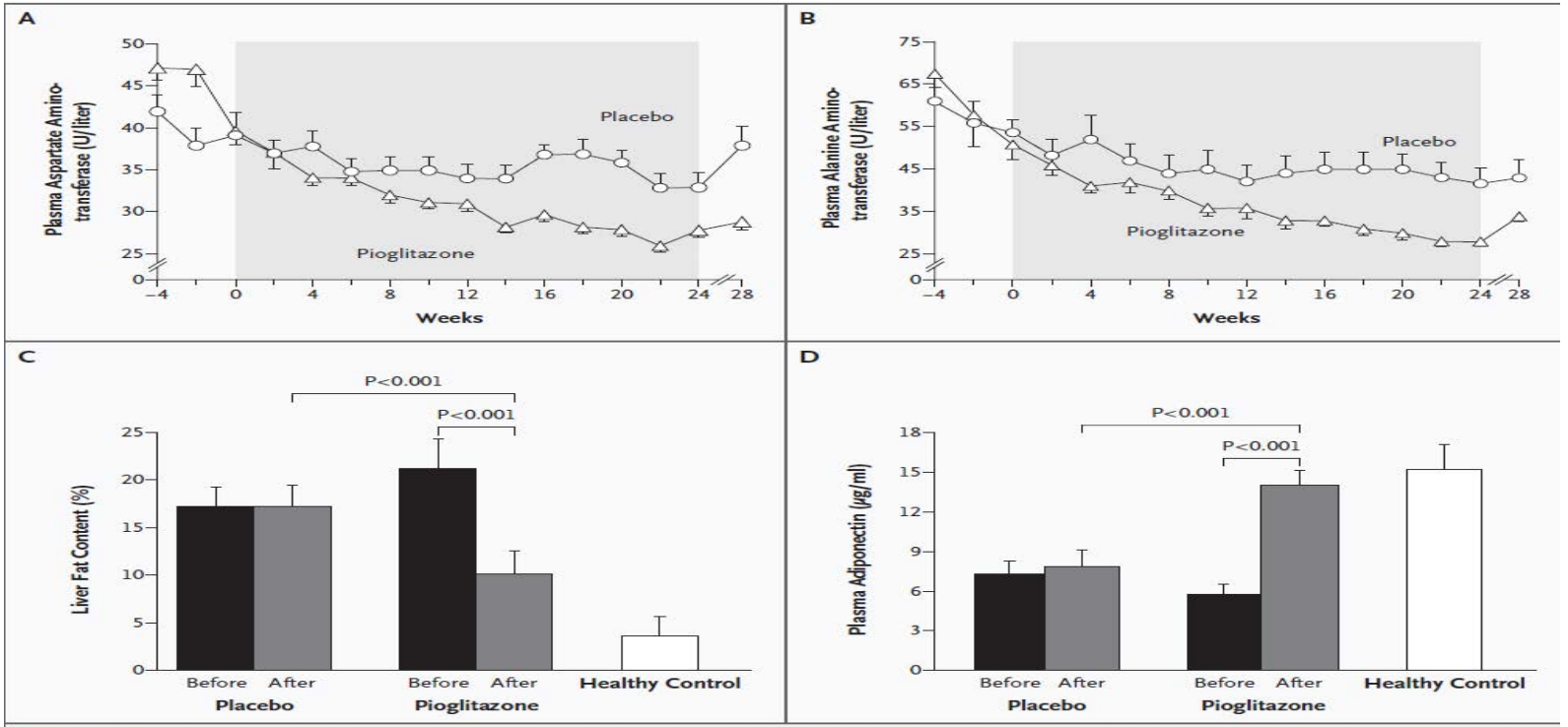


Figure 1. Plasma Aspartate Aminotransferase (Panel A) and Alanine Aminotransferase (Panel B) Concentrations during the Run-in Period (Weeks −4 to 0), the Treatment Period (Weeks 0 to 24, Shaded Area), and the Post-Treatment Follow-up Period (Weeks 24 to 28); Hepatic Fat Content Assessed by Means of Magnetic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

Belfort R NEJM 2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

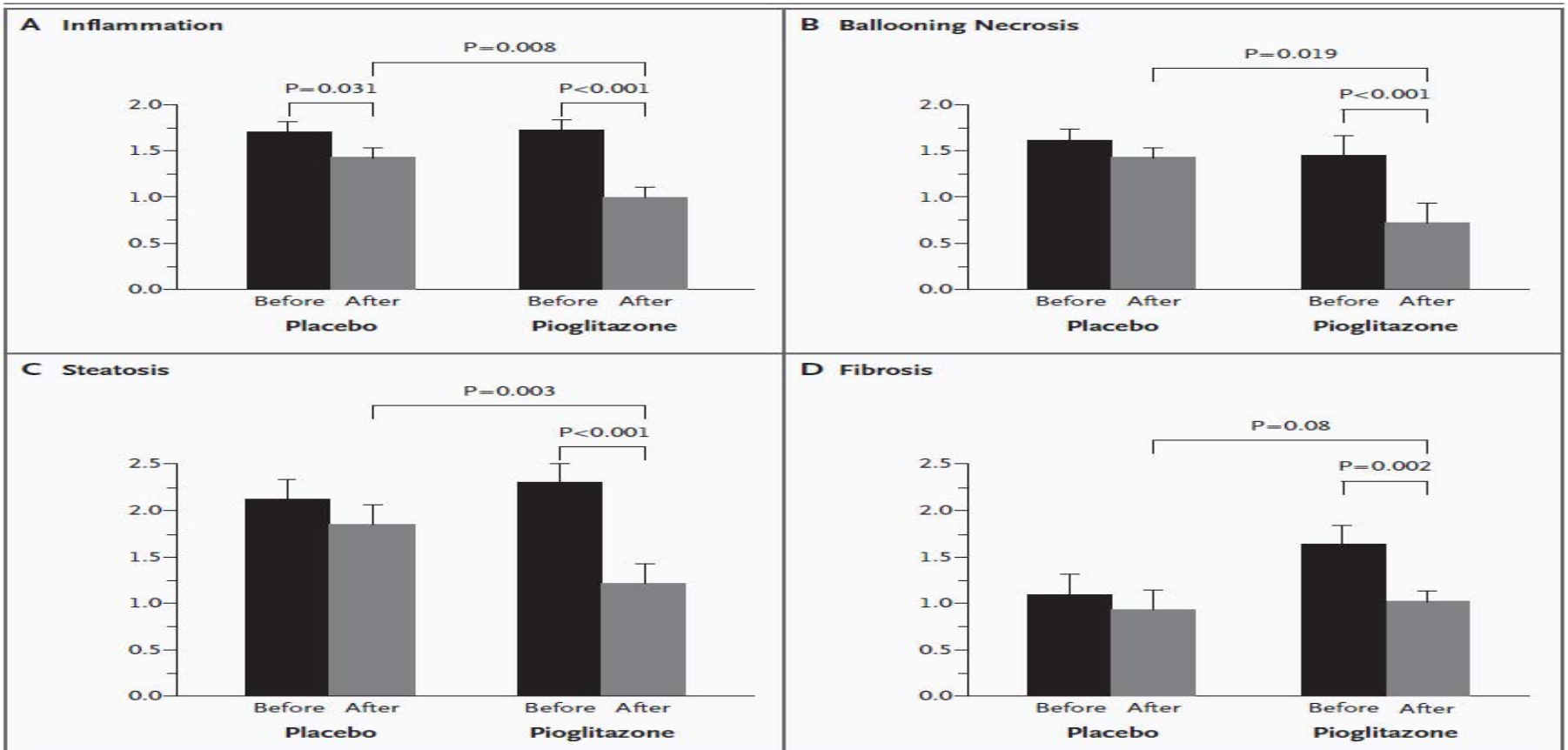


Figure 3. Mean Scores for Inflammation (Panel A), Ballooning Necrosis (Panel B), Steatosis (Panel C), and Fibrosis (Panel D) in Liver Biopsy Specimens.

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.

Belfort R NEJM 2006

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

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)

Chalasani N, Hepatology 2012; 55: 2005-23

Key messages from the trial

Safety perspectives

***Heart failure*:** slightly but not significantly higher rate with pioglitazone. Few cases over 4,5 years (19 PIO vs. 12 SU, i.e. excess of ~1 case per 1000 patient-year, if any). No fatality. *Remark: NYHA 1-4 were excluded from trial.*

***Pathological bone fractures*:** no differences and very few cases over 4,5 years (6 PIO vs. 4 SU, i.e. excess of 0.3 case per 1000 patient-year, if any). *Remark: pathological fractures were focused on.*

***Cancer*:** no significant differences (78 PIO vs. 72 SU, i.e. excess of <1 case per 1000 patient-year, if any; bladder cancer 8 vs. 8 cases).

Insulin sensitizers for the treatment of NASH

A meta-analysis of 15 studies

Outcomes	All insulin sensitizers			Glitazones			Metformin		
	WMD*	95% CI	*P*-value	WMD*	95% CI	*P*-value	WMD*	95% CI	*P*-value
Primary outcome: histological response									
Steatosis	0.40	0.14, 0.65	0.003	0.57	0.36, 0.77	<0.001	−0.19	−0.69, 0.31	0.45
Ballooning	0.16	−0.031, 0.35	0.10	0.36	0.24, 0.49	<0.001	−0.037	−0.19, 0.12	0.64
Inflammation	0.17	−0.15, 0.48	0.29	0.29	−0.05, 0.63	0.09	−0.19	−0.55, 0.17	0.31
Fibrosis	0.24	0.053, 0.42	0.011	0.21	−0.046, 0.46	0.11	0.22	−0.37, 0.81	0.46
Secondary outcome: biochemical and anthropometric response									
ALT	11.9	2.4, 21.5	0.004	16.4	7.70, 25.0	<0.001	13.6	−2.7, 29.9	0.10
BMI	−1.23	−1.61, −0.85	<0.001	−0.90	−1.59, −0.22	0.010	0.75	−0.97, 2.48	0.39

WMD, weighted mean difference; CI, confidence interval; DM, diabetes mellitus; ALT, alanine aminotransferase; BMI, body mass index.

* WMD: a positive WMD indicates greater improvement in the treatment group compared with controls.

Treatment of NASH with metformin, did not demonstrate a significant histological and biochemical benefit.

Rakoski MO et al., Aliment Parmacol Ther 32: 1211-21, 2010

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

Recommendation

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)

Chalasani N, Hepatology 2012; 55: 2005-23

NAFLD e DPP-IV

- L'espressione del mRNA del DPP-IV epatico è significativamente più alto nei pz con NAFLD rispetto ai soggetti normali.
  (Miyazaki M Mol Med Rep 2012; 5:729-33)
- L'attività della DPP-IV sierica e l'espressione epatica della DPP-IV sono correlate con la steatosi epatica e con il grading della NAFLD
  (Balban YH Ann Hep 2007; 6: 242-50)
- Gli inibitori della DPP-IV sarebbero in grado di ridurre il contenuto di TGL e l'espressione di geni coinvolti nella lipogenesi e nella gluconeogenesi, come dimostrato su modelli animali
  (Shirakawa J, Diabetes 2011; 60: 1246-1257; Yilmaz T Acta GastrBel 2012; 75: 240-44)

- E' stato pubblicato un caso di NAFLD refrattaria alle terapie, trattata con successo con sitagliptin
  (Itou M, Case Rep Gastr 2012; 6: 538-44)

Sitagliptin as a novel treatment agent for NAFLD in patients with Type 2 Diabetes Mellitus

n. 30 NAFLD patients with type 2 DM.
NAFLD was diagnosed by ultrasonography. Sitagliptin (50mg/body/day) for 4 months.

	baseline	4 weeks	8 weeks	12 weeks	16 weeks
AST	44.1 ± 22.0	36.5 ± 18.9***	34.1 ± 20.4***	32.9 ± 20.2***	30.6 ± 19.3***
ALT	55.6 ± 26.9	43.7 ± 21.9***	40.1 ± 23.2***	39.3 ± 22.3***	35.9 ± 22.6***
γ-GTP	60.6 ± 31.9	53.8 ± 34.0*	49.8 ± 33.3**	46.5 ± 28.2***	43.2 ± 26.1***
BMI	26.7 ± 5.30	26.8 ± 4.89	26.9 ± 4.84	26.8 ± 4.87	26.8 ± 4.84
HbA1c	8.12 ± 1.81	7.52 ± 1.16**	7.19 ± 1.07**	6.98 ± 1.00***	6.81 ± 0.93***

Data are means ± SD. *$p<0.05$, **$p<0.01$, ***$p<0.001$ baseline *vs.* 4 weeks, 8 weeks, 12 weeks and 16 weeks.
AST: asparate aminotransferase, ALT: alanin aminotransferase, γ-GTP: γ-glutamyl transpeptidase, BMI: body mass index, HbA_{1c}: he moglobin A_{1c}.

Iwasaki T. Hepato-Gastroenterology 2011; 58; 2103-05

Incretin based therapies: a novel treatment approach for non-alcoholic fatty liver disease

- Sitagliptin as a novel treatment agent for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: ***significant decreases of serum AST, ALT and γ-GTP levels were observed after 4 months of treatment with sitagliptin***
- Effects of sitagliptin in diabetic patients with nonalcoholic steatohepatitis: ***sitagliptin ameliorates liver enzymes and hepatocyte ballooning in NASH patients with typev 2 DM***

Iwasaki T et al., Hepatogastroenterology 58: 2103-5, 2011

Yilmaz Y et al., Acta Gastroenterol Belg 75: 240-4, 2012

NAFLD e GLp-1 analoghi

- Gli analoghi del GLP-1 migliorano il quadro epatico sia indirettamente (miglioramento del compenso metabolico, calo ponderale, miglioramento della sensibilità insulinica) sia direttamente (ossidazione degli acidi grassi, inbizione del Fibroblast Growth Factor 21 a livello epatico)

- In uno studio condotto su pazienti in sovrappeso e NASH, diagnosticata tramite biopsia epatica, trattati per 48 settimane con liraglutide o placebo, il 39 % dei pz trattati con liraglutide ha mostrato una risoluzione della NASH (evidenziata con biopsia) vs il 9% del gruppo di controllo.

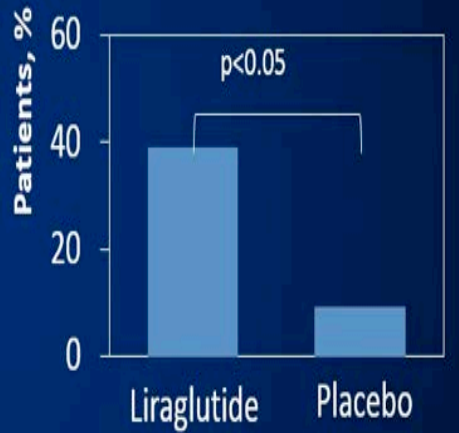
Liraglutide in NAFLD/NASH

- GLP-1 RA that lowers plasma glucose by ↑insulin secretion and ↓ appetite and stomach emptying
- Controversial GLP-1 signaling in hepatocytes
- A 48-week phase 2 RCT in 52 patients with biopsy-proven NASH, A1c <9%; patient characteristics well matched
- Interevention: liraglutide or placebo (for up to 1,8 mg QD) for 48 weeks (follow-up at 72 weeks)

Baseline characteristics

Characteristics	Liraglutide (n=23)	PBO (n=22)
Mean (SD) NAS	4.9 (0.9)	4.8 (0.9)
Mean (SD) Kleiner fibrosis	2.3 (0.9)	2.3 (1.3)
F0–2, n (%)	14 (54%)	11 (42%)
F3–4, n (%)	12 (46%)	15 (58%)

Primary endpoint: NASH resolution with no worsening of fibrosis



Secondary endpoints

Endpoint	Liraglutide (n=23)	PBO (n=22)
Mean (SD) change, Kleiner fibrosis	-0.2 (0.8)	0.2 (1.0)
Improvement, n (%)	6 (26.1)	3 (13.6)
Worsening, n (%)	2 (8.7)*	8 (36.4)

*p<0.05 vs placebo

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

Clinical practice recommendations regarding the use of glucose-lowering agents in diabetic patients with various degrees of hepatic impairment

medications	mild HI	moderate HI	severe HI	feared adverse event
biguanides	yes	caution	No use	Lactic acidosis
sulfonylureas	yes	caution	No use	hypoglycemia
glinides	yes	caution	No use	hypoglycemia
alpha-glucosidase inhibition	yes	Probably yes	Probably yes	hyperamonemia
thiazolidinedones	yes	caution	No use	Hepatotoxicity?
DPP-4 inhibitors	yes	Probably yes	Caution	Unknown,no clinical experience
SGLT2 inhibitors	Yes	caution	No use	Unknown,no clinical experience
GLP-1 receptor agonists	Yes	Probably yes	Caution or no use	Unknown, no clinical experience
insulin and insulin analogs	yes	yes	Yes, caution	hypoglycemia

Scheen AJ ,Expert Opin Drug Metab Toxicol, 2014; 10(6): 839-57

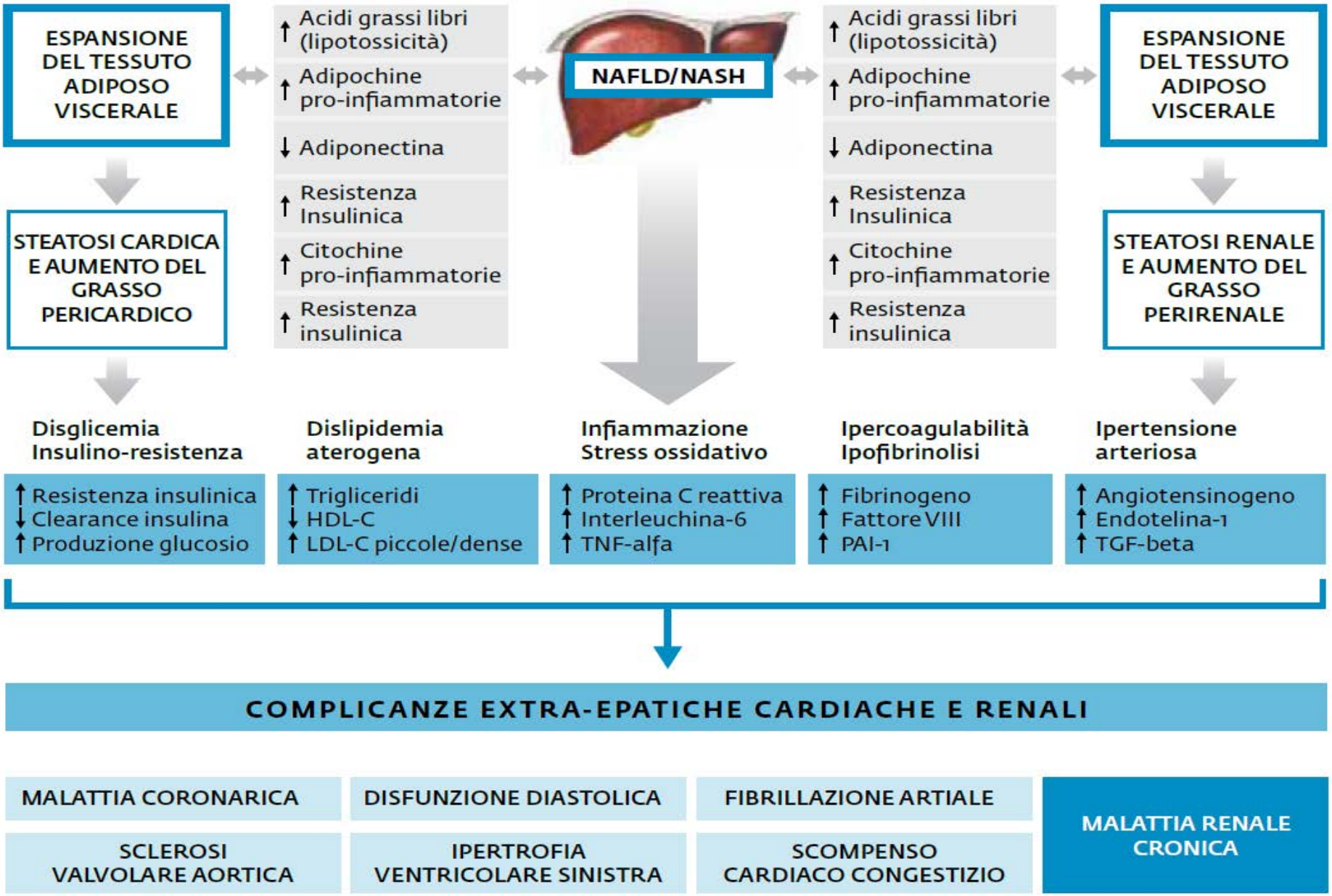
Caso clinico

Il paziente inizia:

- metformina 850 mg, 1cp dopo pranzo e 1 cp dopo cena
- analogo del GLP-1

e torna in ambulatorio dopo 3 mesi

	prima	3 mesi dopo
Peso (Kg)	92	86
BMI (kg/m^2)	32	29.7
CV (cm)	109	102
P.A. (mmHg)	150/80	130/75
FPG mg/dl	138	112
HbA_{1c}	7.5%	6.9%
Creatinina mg/dl	1,21	1,01
AST (vn<40 U/I)	36	26
ALT (v.n.<41U/I)	52	35
GGT (v.n.: 55 U/l)	250	128
Colesterolo totale	208	198
HDL	46	50
TGL	150	95



Abbreviazioni: PAI-1: plasminogen activator inhibitor-1, TGF: tumour growth factor, TNF: tumour necrosis factor