NAFLD e farmaci antiiperglicemic

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Disclosures

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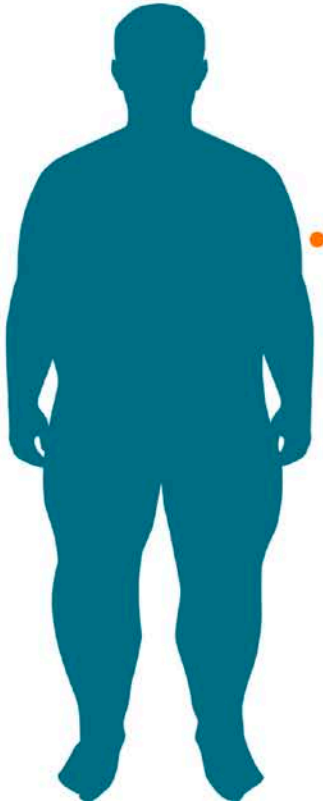
Honoraria: Novo Nordisk

Clinical Studies: Genfit, Intercept, Novo Nordisk

Fattori di rischio per NAFLD



- Cardiovascular Disease*
- Malignancy*
- Obesity
- Diabetes
- Metabolic Syndrome
- Cerebrovascular Disease
- Chronic Kidney Disease
- Polycystic Ovary Syndrome
- Obstructive Sleep Apnea

*Primary cause of mortality.

Obesity

Obesity is linked not only to diabetes, MS, and CVD, but also to NAFLD and NASH.

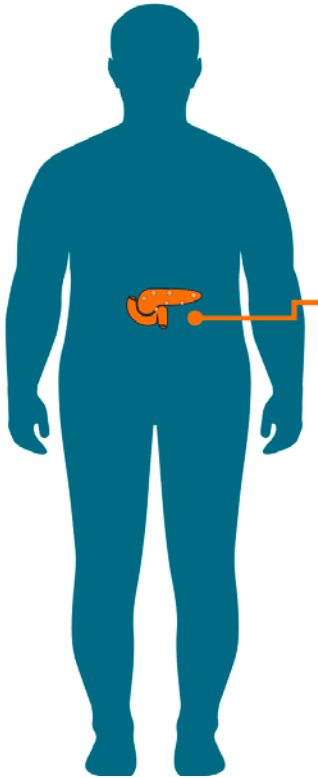
The close link between obesity and NAFLD/NASH is supported by treatment via weight loss, which can even result in resolution of NASH and fibrosis regression.

Obesity is a key contributor to lipotoxicity, as well as subsequent liver inflammation and fibrosis, through the release of FFAs.

Patients with obesity have a higher prevalence of NAFLD and NASH and a higher rate of fibrosis progression than patients who are not obese.

Modified from A. Sanyal

Fattori di rischio per NAFLD



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Diabetes

Patients with diabetes frequently show more fibrosis compared with patients without diabetes; a study indicates that 15% to 20% of patients with diabetes and steatosis have moderate to severe fibrosis.

Obesity, NAFLD, and insulin resistance are each independently associated with a 2-fold risk for diabetes. If all 3 are present, there is a 14-fold risk for diabetes.

Modified from A. Sanyal

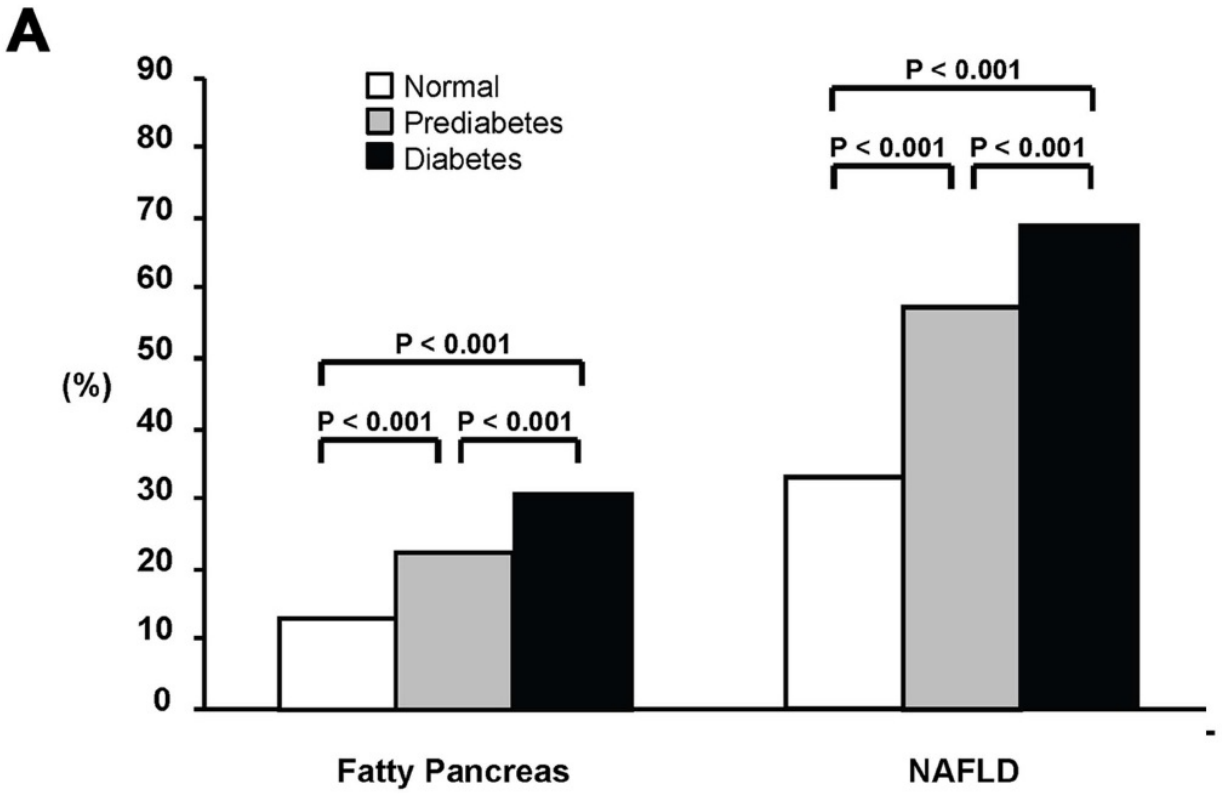
Predittori clinici di rischio per NASH in pazienti con NAFLD

Characteristic	Outcome
Advanced age*	Greater duration of disease
Sex	Postmenopausal women experience accelerated disease
Race	↑ Prevalence, severity in Hispanic, Asian patients; ↓ Prevalence, severity in black patients
Hypertension* **central obesity, dyslipidemia (↑ TG, ↓ HDL)** **Diabetes***	66% prevalence of bridging fibrosis if older than 50 yrs of age and obese or diabetic[5,6]
AST/ALT ratio > 1, low platelets	Indicators of NASH cirrhosis
Persistently elevated ALT	Can be associated with greater risk of disease progression

*** Strongest predictors of advanced disease, regardless of liver enzyme elevation.**

Younossi, Hepatology 2016, Ratziu Gastro 2000, Angulo Hepatology 1999, Neuschwander-Tetri, Hepatology. 2010, McPherson, J Hepatology 2015.

The Association between Nonalcoholic Fatty Pancreas Disease and Diabetes



Il grasso pancreatico si associa in modo dose-dipendente con la ridotta secrezione insulinica (β-cell index)

β-cell index si riduce progressivamente con lo stadio della fibrosi

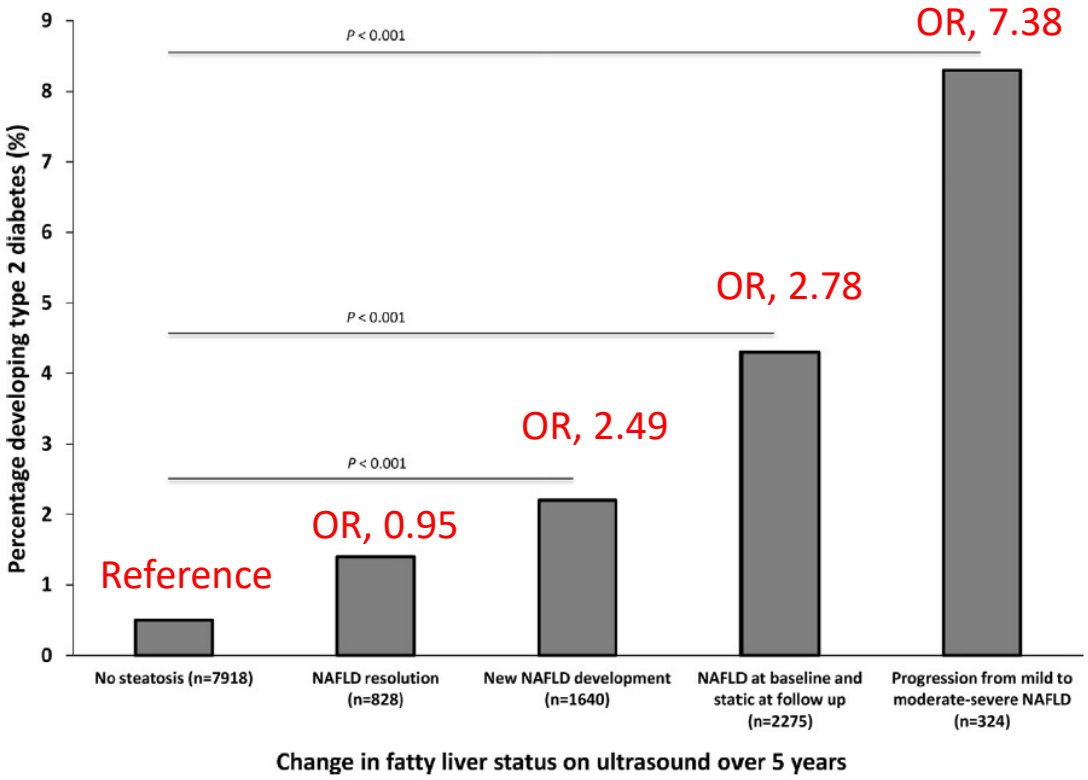
Ou, Plos One 2013

Incidenza e remissione della steatosi epatica sono predittivi di DM2

A total of 13 218 people without T2DM at baseline from a Korean cohort examined after 5 years, using a retrospective study design.

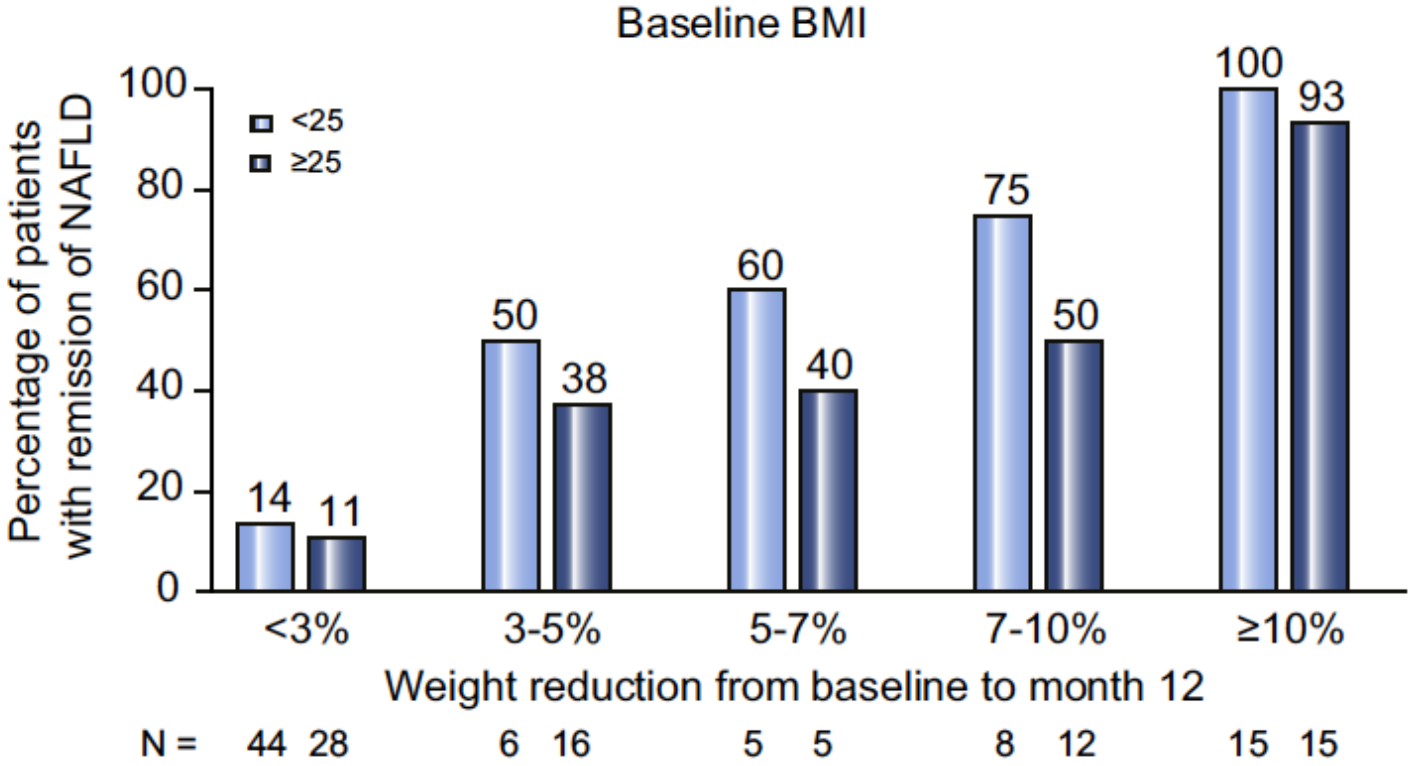
Fatty liver status assessed at baseline and f-up as absent, mild, or moderate/severe

Model adjusted for baseline age; sex; BMI; glucose; insulin; triglycerides; HDL-C; systolic BP; alcohol use; smoking; physical activity; change in BMI between baseline and follow-up; and ALT, AST, and GGT.



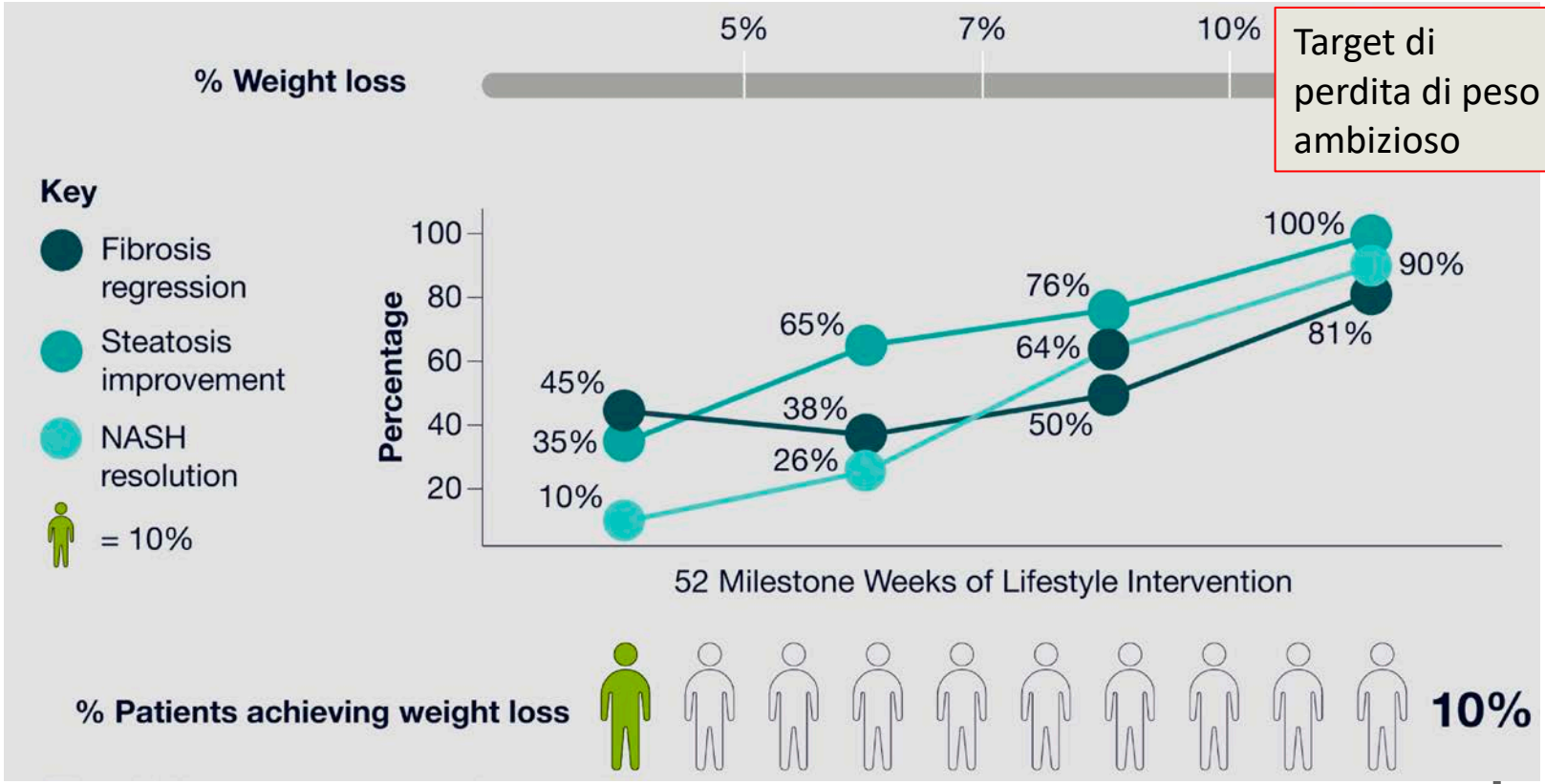
Sung, J Clin Endocrinol Metab 2013

Beneficio della modifica dello stile di vita in pazienti non obesi con NAFLD



Wong, J Hepatol 2018

Modifiche nello stile di vita nella NAFLD



Target di perdita di peso ambizioso

Modified from A. Sanyal

Dall'aula …… al web

Group-based program

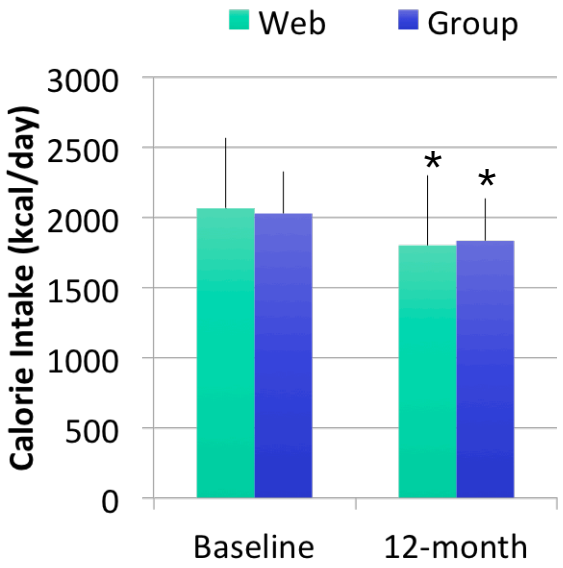
Intervento con gruppi in aula
Partecipazione dei pazienti NAFLD in programmi strutturati sulla modifica dello stile di vita può essere problematica causa difficoltà in assentarsi dal lavoro, distanza dal Centro e poco tempo a disposizione

Web-based program

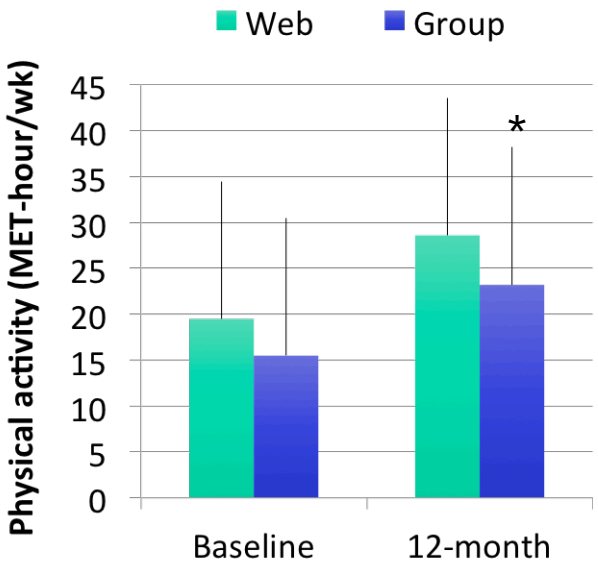
Programmi individuali via Web possono aiutare a mantenere i contatti tra pazienti motivati e terapisti, e foniscono strumento per controllare la aderenza

Web-based counseling for NAFLD – Lifestyle changes

Calorie intake

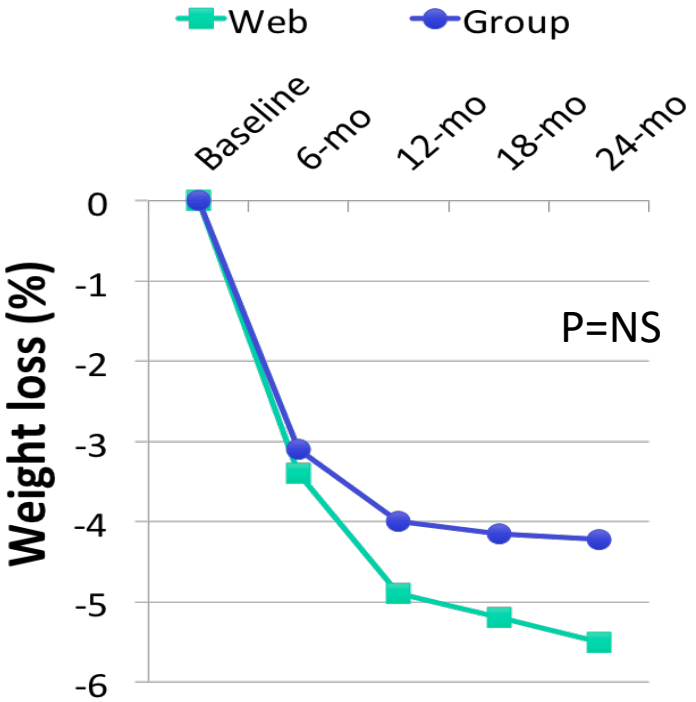


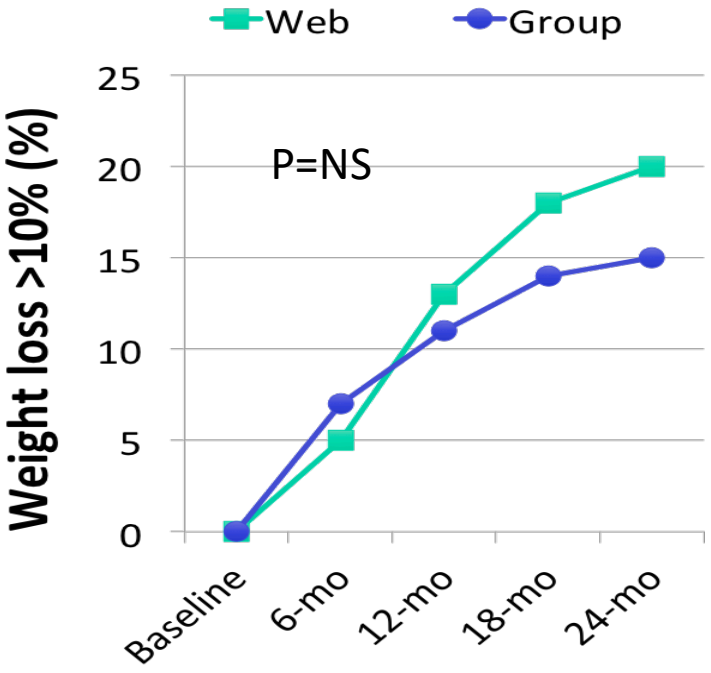
Physical activity



Mazzotti, J Hepatol 2018

Web-based counseling for NAFLD – Weight loss





Mazzotti, J Hepatol 2018

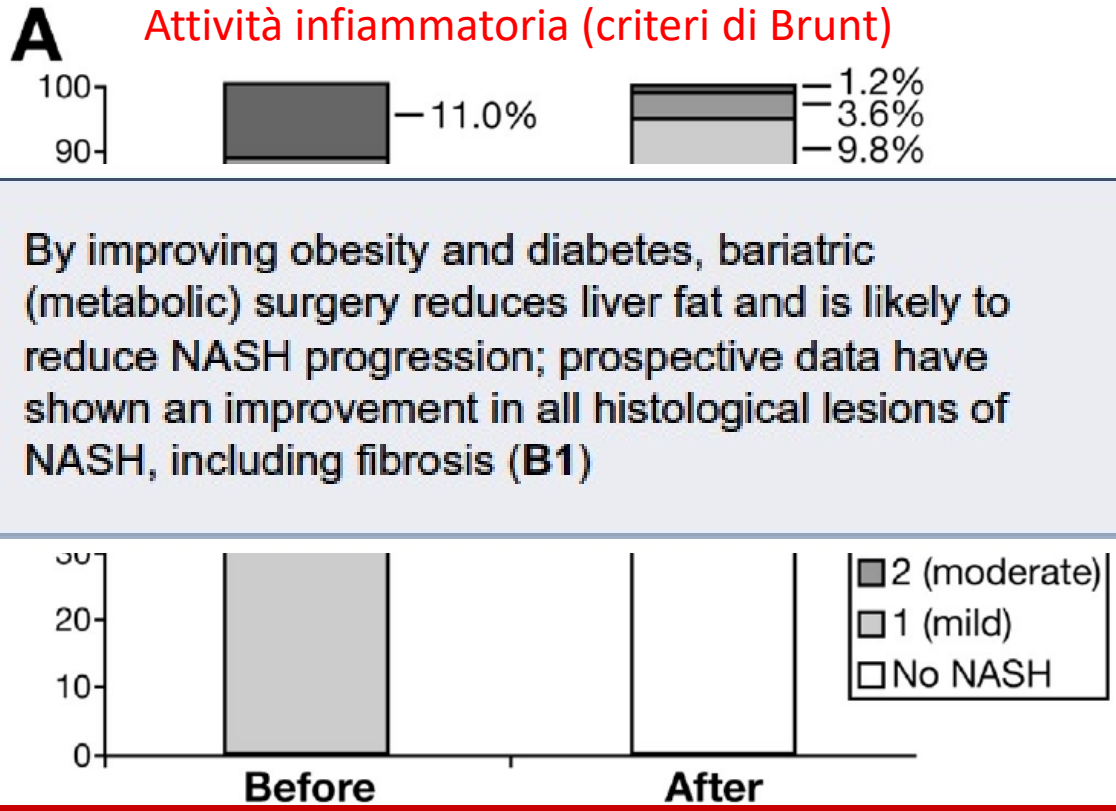
Terapie di gruppo a distanza

La pandemia COVID-19 ha reso necessaria la erogazione della terapia di gruppo in remoto utilizzando piattaforme di didattica a distanza.

Raccolta dati è in corso, impressioni preliminari rilevano vantaggi e svantaggi:

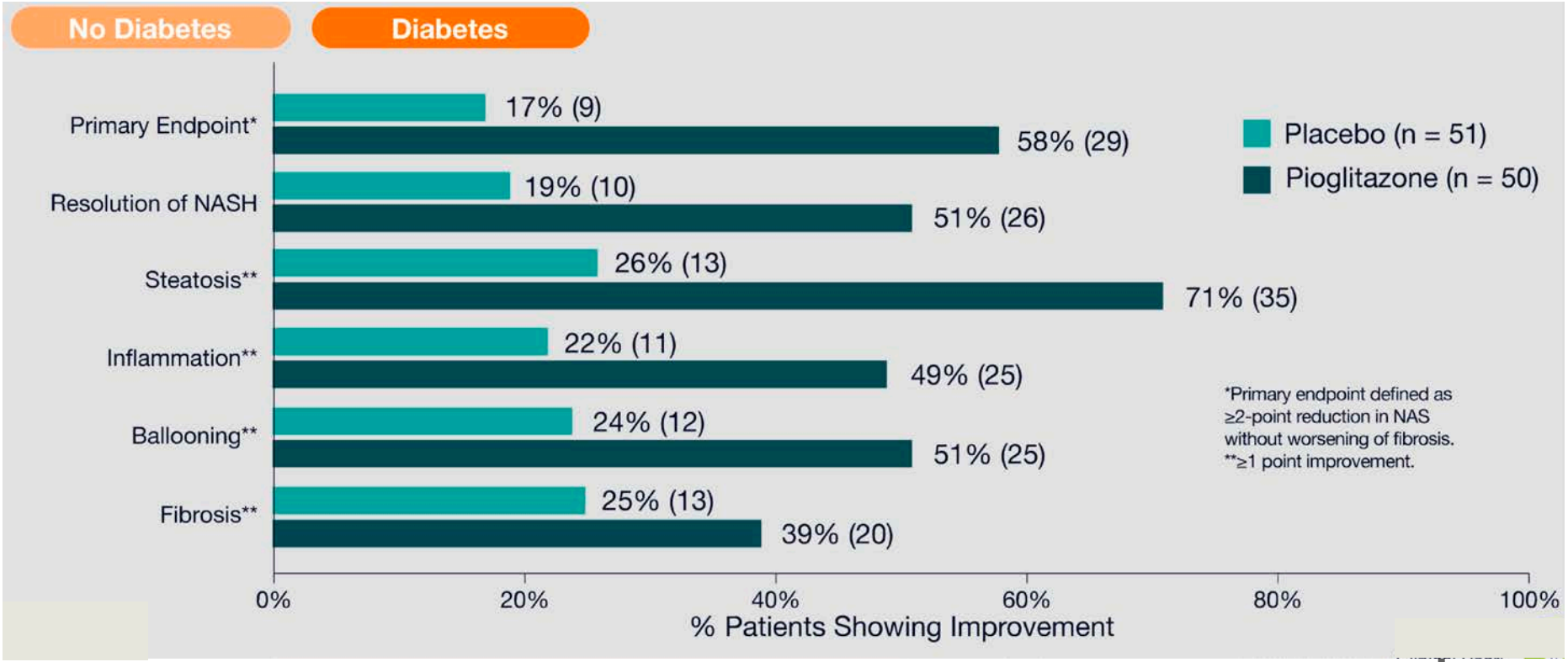
- quasi la metà dei pazienti non ha confidenza adeguata con tecnologie informatiche di base o connessione adeguata e rinuncia (pazienti anziani e basso livello socio economico)
- ottima adesione soprattutto in orario tardo pomeridiano di pazienti lavoratori con livello socio economico medio od alto

Chirurgia bariatrica e risoluzione della NASH



Lassailly, Gastroenterology 2015

Trattamento con pioglitazone delle NAFLD con associato DM2



Modified from A. Sanyal

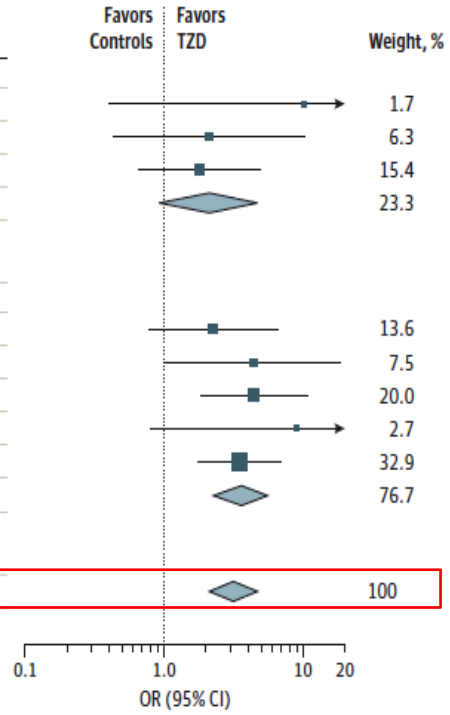
Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis

A Improvement in fibrosis of any stage

Source	TZD No. of Events	TZD No. of Patients	Contro No. of Events
Rosiglitazone maleate			
Idilman et al,[19] 2008	2	11	0
Omer et al,[21] 2010	3	20	3
Ratziu et al,[18] 2008	5	32	5
Total (95% CI)	10	63	8
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.78$; $P=.68$; $I^2=0\%$			
Overall effect: $z=0.33$; $P=.74$			
Pioglitazone hydrochloride			
Aithal et al,[17] 2008	9	31	6
Belfort et al,[16] 2006	12	26	7
Cusi et al,[12] 2016	20	50	13
Sanyal et al,[15] 2004	2	10	1
Sanyal et al,[20] 2010	35	80	26
Total (95% CI)	78	197	53
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=.12$; $P>.99$; $I^2=0\%$			
Overall effect: $z=2.60$; $P=.009$			
Total (95% CI)	88	260	61
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.40$; $P>.99$; $I^2=0\%$			
Overall effect: $z=2.52$; $P=.01$			

B Induction of NASH resolution

Source	TZD No. of Events	TZD No. of Patients	Controls No. of Events	Controls No. of Patients	Odds Ratio (95% CI)
Rosiglitazone maleate					
Idilman et al,[19] 2008	4	11	0	8	10.20 (0.47-222.45)
Omer et al,[21] 2010	5	20	3	22	2.11 (0.43-10.28)
Ratziu et al,[18] 2008	16	32	11	31	1.82 (0.66-5.00)
Total (95% CI)	25	63	14	61	2.14 (0.94-4.86)
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.11$; $P=.58$; $I^2=0\%$					
Overall effect: $z=1.82$; $P=.07$					
Pioglitazone hydrochloride					
Aithal et al,[17] 2008	14	31	8	30	2.26 (0.77-6.63)
Belfort et al,[16] 2006	11	26	3	21	4.40 (1.03-18.74)
Cusi et al,[12] 2016	26	50	10	51	4.44 (1.83-10.78)
Sanyal et al,[15] 2004	5	10	1	10	9.00 (0.81-100.14)
Sanyal et al,[20] 2010	38	80	17	83	3.51 (1.76-7.01)
Total (95% CI)	94	197	39	195	3.65 (2.32-5.74)
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.56$; $P=.82$; $I^2=0\%$					
Overall effect: $z=5.61$; $P<.001$					
Total (95% CI)	119	260	53	256	3.22 (2.17-4.79)
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=3.90$; $P=.79$; $I^2=0\%$					
Overall effect: $z=5.79$; $P<.001$					

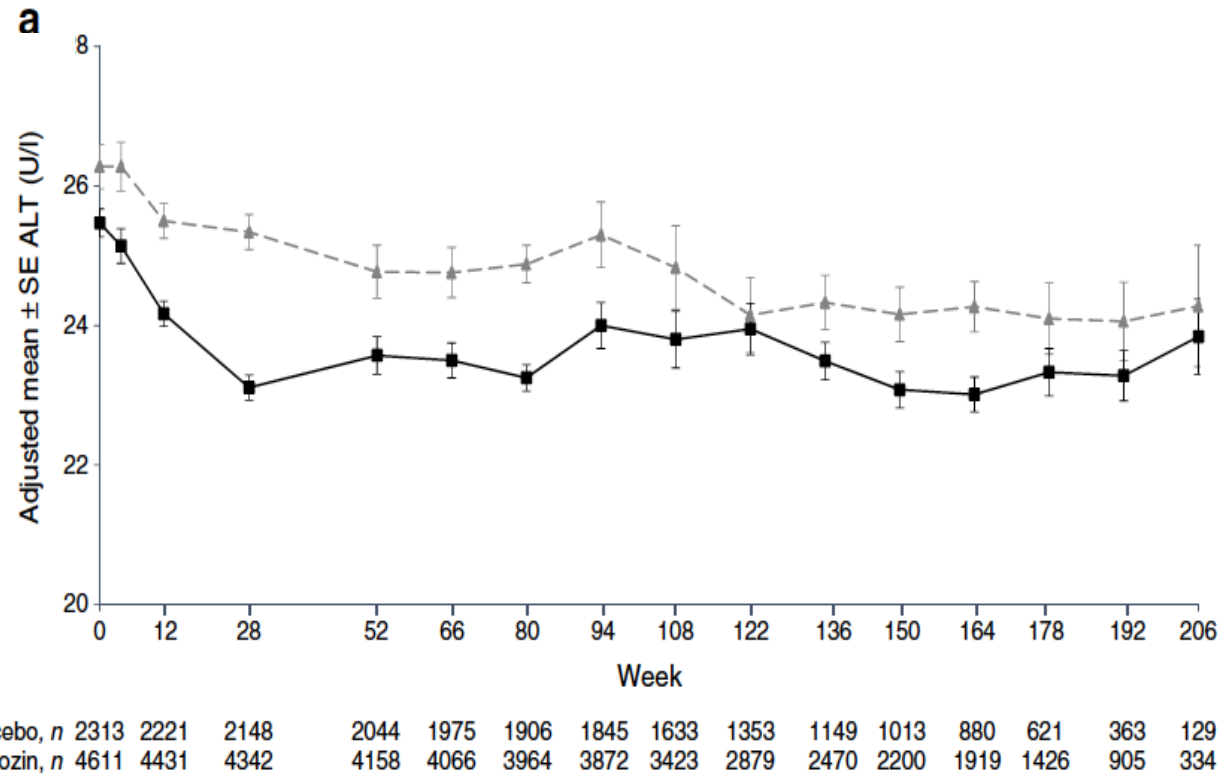


Musso, JAMA 2017

Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial

Empagliflozin riduce le ALT nei soggetti con DM2, in un pattern (ALT> AST) potenzialmente coerente con una riduzione del grasso epatico, specialmente quando i livelli di ALT sono elevati.

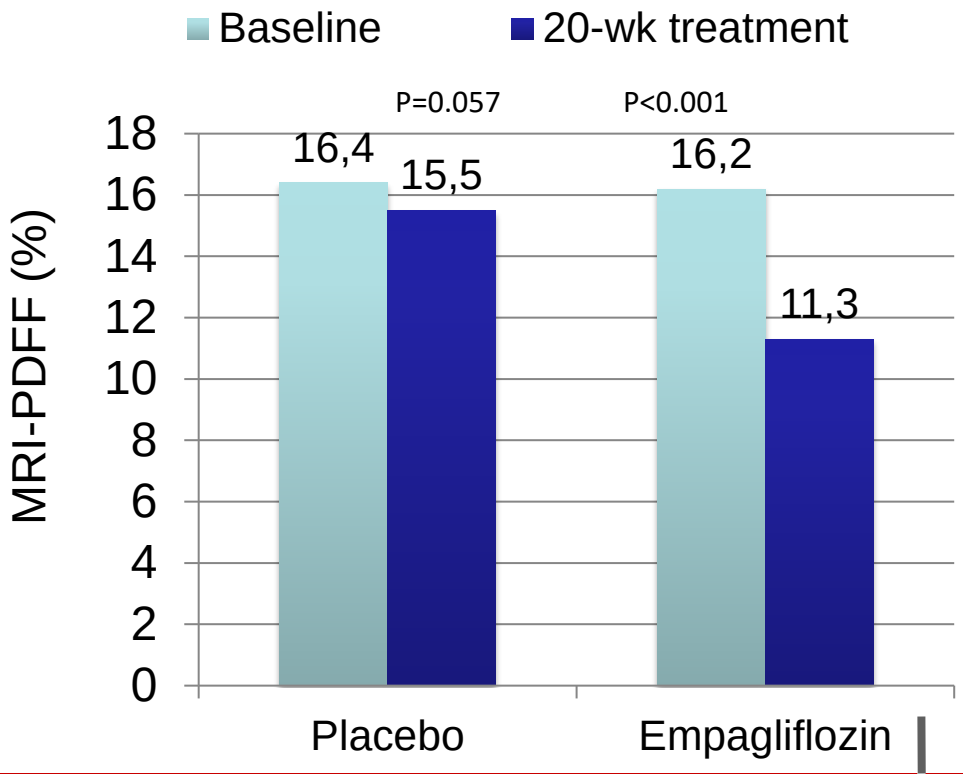
La riduzione dei livelli di ALT era largamente indipendente dalle modifiche del peso o dei livelli di HbA1c.



Sattar, Diabetologia 2018

Empagliflozin nella NAFLD (E-LIFT trial)

- 50 pts. con DM2 e NAFLD randomizzati al gruppo EMPA (trattamento standard per DM2 più empagliflozin 10mg/die) o al gruppo di controllo (trattamento standard, no EMPA) per 20 settimane.
- Liver fat content misurato tramite MRI-PDFF significativamente ridotto nel solo gruppo EMPA
- Differenza significativa tra I gruppi nei valori di ALT (P = 0.005) ma non differenze significative nei livelli di AST (P = 0.212) e GGT (P = 0.057).



Kuchay, Diabetes Care 2018

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide *vs* placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

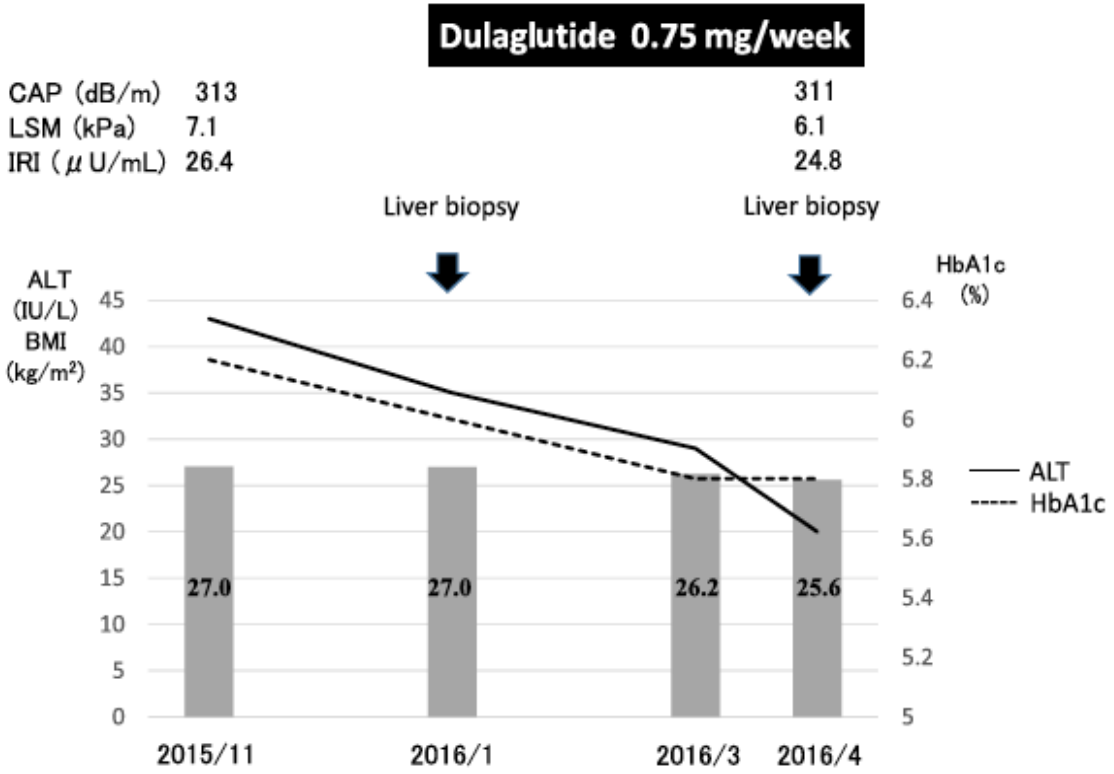
Questo studio randomizzato e controllato con placebo è il primo sulla classe degli analoghi del GLP-1 in pazienti con NASH. Liraglutide ha raggiunto l'endpoint primario della risoluzione istologica della NASH senza peggioramento della fibrosi. Oltre ai miglioramenti nella steatosi istologica e nel balloning degli epatociti, un minor numero di pazienti che ricevevano liraglutide presentava una progressione della fibrosi rispetto al PL. Liraglutide ha migliorato diversi componenti chiave della SM, inclusi il peso e il controllo glicemico, rilevanti per il rischio CV

Armstrong, Lancet 2015

Effect of 12-week dulaglutide therapy in Japanese patients with biopsy-proven non-alcoholic fatty liver disease and type 2 diabetes mellitus

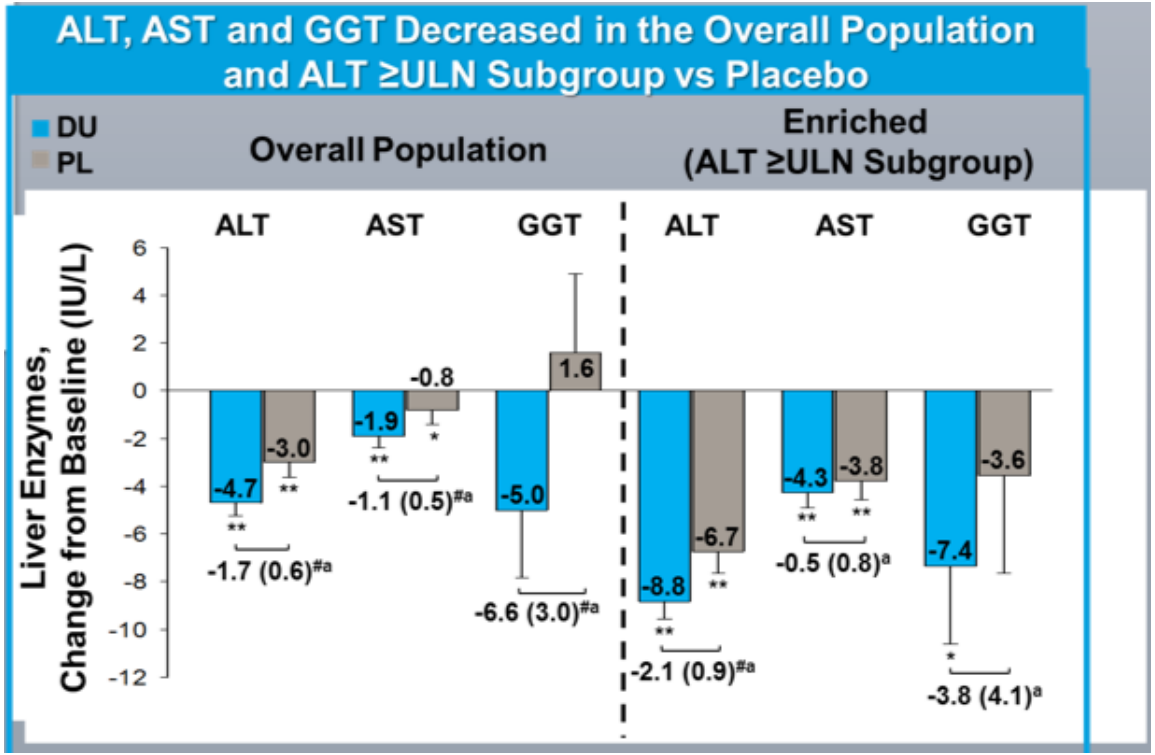
15 patients refractory to diet received once weekly dulaglutide 0.75 mg for 12 wks. In five patients, transient elastography and body composition were also evaluated before and after the treatment. AST-ALT significantly decreased in the whole group, as well as total body fat mass and liver stiffness

Dulaglutide, a new glucagon-like peptidase-1 receptor agonist, could be a novel promising agent for the treatment for NAFLD patients with T2DM



Seko, Hepatol Res 2016

Effetto di dulaglutide su LFTs (studi Award)

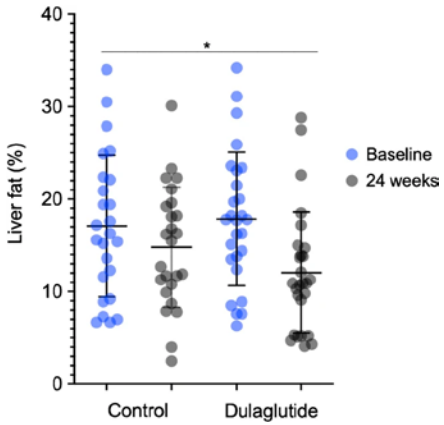


Dulaglutide Decreases Liver Enzymes in People with Type 2 Diabetes: A Post Hoc Analysis of the AWARD Programme

Axel Haupt[1], Naveed Sattar[2], Luis-Emilio Garcia-Pérez[1], Imre Pavo[1], Maria Yu[1], Kenneth E. Robertson[1], Kenneth Cusi[3]
[1]Eli Lilly and Company, Indianapolis, USA; [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [3]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Florida, Gainesville, USA

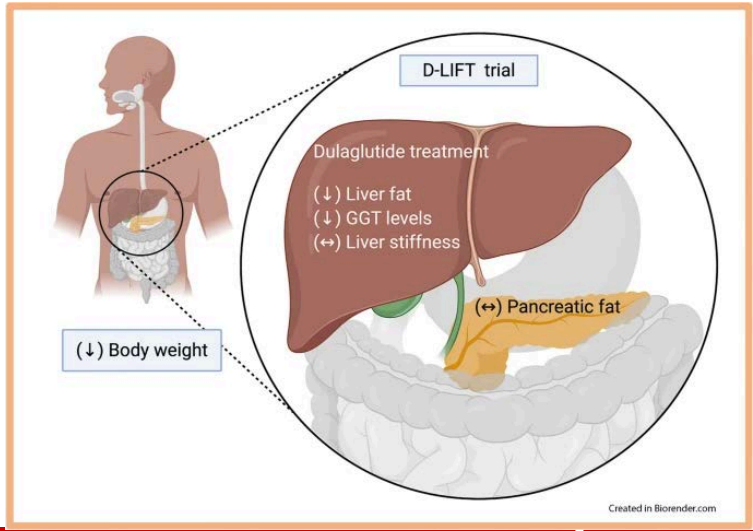
Dulaglutide nella NAFLD (D-LIFT Trial)

52 pazienti con DM2 e valore basale di LFC valutato con MRI-densità protonica (PDFF) di ≥6,0% randomizzati (1: 1) a ricevere dulaglutide 0,75 mg/sett. per 4 sett. ➔1,5 mg/sett. per 20 sett. in aggiunta al trattamento standard o al solo trattamento standard



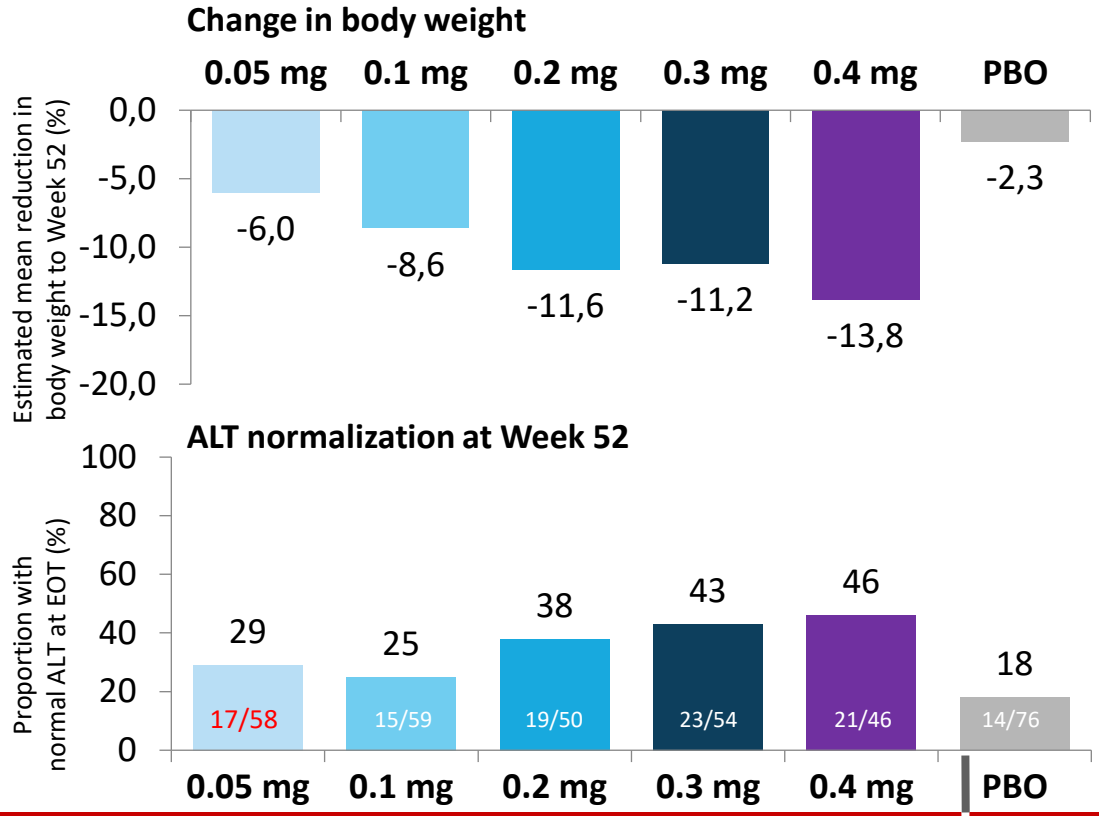
I trattati con Dulaglutide hanno mostrato una riduzione del LFC di 2.6 volte superiore al placebo (diff.−3,5% (IC 95%: da −6,6 a −0,4; P = 0,025) una maggiore riduzione dei livelli di GGT (diff. media tra i gruppi: −13,1 U / l [IC 95%: −24,4 −1,8]; P = 0,025)

Non differenze in ALT, pancreatic fat content e stiffness epatica



Effecto di semaglutide sugli enzimi epatici in soggetti con obesità ed elevazione ALT

Baseline characteristics	Subjects with elevated ALT (n=499)	Subjects with normal ALT (n=458)
Age, y	48 (18–76)	47 (19–86)
Male, n (%)	187 (37.5)	151 (33.0)
Weight, kg	106.9 (70.5–216.3)	107.8 (70.2–243.7)
BMI, kg/m^2	37.4 (29.7–77.1)	37.9 (29.7–80.3)
HbA1c, %	5.5 (4.3–6.6)	5.5 (4.2–7.0)
Total cholesterol, mmol/L	5.2 (2.7–9.7)	5.0 (2.6–10.3)
LDL-C, mmol/L	3.2 (1.1–6.2)	3.0 (0.8–7.2)
HDL-C, mmol/L	1.2 (0.5–2.4)	1.3 (0.7–2.9)
TG, mmol/L	1.6 (0.5–11.9)	1.4 (0.4–9.9)
ALT, IU/L	34 (20–313)	17 (3–30)
AST, IU/L	24 (12–272)	16 (8–62)
Impaired fasting glucose, n/N (%)	76/499 (15.2)	57/457 (12.5)



Newsome et al, Aliment Pharmacol Ther 2019

Semaglutide nella NAFLD

Dopo i dati promettenti dello studio di fase 2 che ha testato semaglutide in pazienti con NASH, Novo Nordisk ha annunciato il completamento dello studio di fase 2 multicentrico, randomizzato, in doppio cieco, controllato con placebo, della durata di 72 settimane, che ha testato semaglutide s.c. in 320 pazienti.
Nello studio i pazienti con NASH sono stati randomizzati a ricevere 1 di 3 diverse dosi di trattamento una volta al giorno (0,1 mg, 0,2 mg o 0,4 mg) o placebo. I ricercatori hanno eseguito biopsie epatiche al basale e alla fine dello studio.
Dei 320 pazienti, 230 dei partecipanti avevano fibrosi F2-F3.
I ricercatori hanno ricercato un endpoint primario della risoluzione della NASH senza peggioramento della fibrosi epatica. L'endpoint primario è stato raggiunto per tutte le dosi del gruppo di trattamento rispetto al placebo.
Per i pazienti che ricevevano 0,4 mg di semaglutide per via sottocutanea, 33 dei 56 (59%) pazienti avevano una risoluzione della NASH, mentre solo 10 dei 58 (17%) pazienti trattati con placebo avevano raggiunto la risoluzione della NASH.

novo nordisk

company announcement

Semaglutide 2.4 mg demonstrates superior and sustained weight loss versus placebo and in addition a 17.4% weight loss after 68 weeks in STEP 4 trial

Bagsværd, Denmark, 13 May 2020 – Novo Nordisk today announced headline results from STEP 4, the first completed phase 3a trial in the STEP programme. STEP 4 is a randomised, double-blind, multicentre, placebo-controlled, withdrawal trial exploring sustained weight management with semaglutide vs placebo. The 68-week trial investigated the effect of once-weekly subcutaneous (sc) semaglutide 2.4 mg on body weight in 902 people with obesity or overweight with comorbidities. After the 20-week run-in period, the 803 people reaching the target dose of semaglutide 2.4 mg had reduced their mean body weight from 107.2 kg to 96.1 kg and were randomised to continued treatment with either once-weekly sc semaglutide 2.4 mg or placebo for 48 weeks.

The trial achieved its primary objective by demonstrating that in all people randomised[1], continued treatment with sc semaglutide 2.4 mg for 48 weeks (after the run-in period) resulted in an additional mean weight loss of 7.9%, from a mean baseline body weight at randomisation of 96.1 kg, whereas people on placebo regained 6.9% of the body weight. The treatment difference was statistically significant. People who received sc semaglutide 2.4 mg for 68 weeks (run-in period plus 48 weeks) achieved a total weight loss of 17.4%.

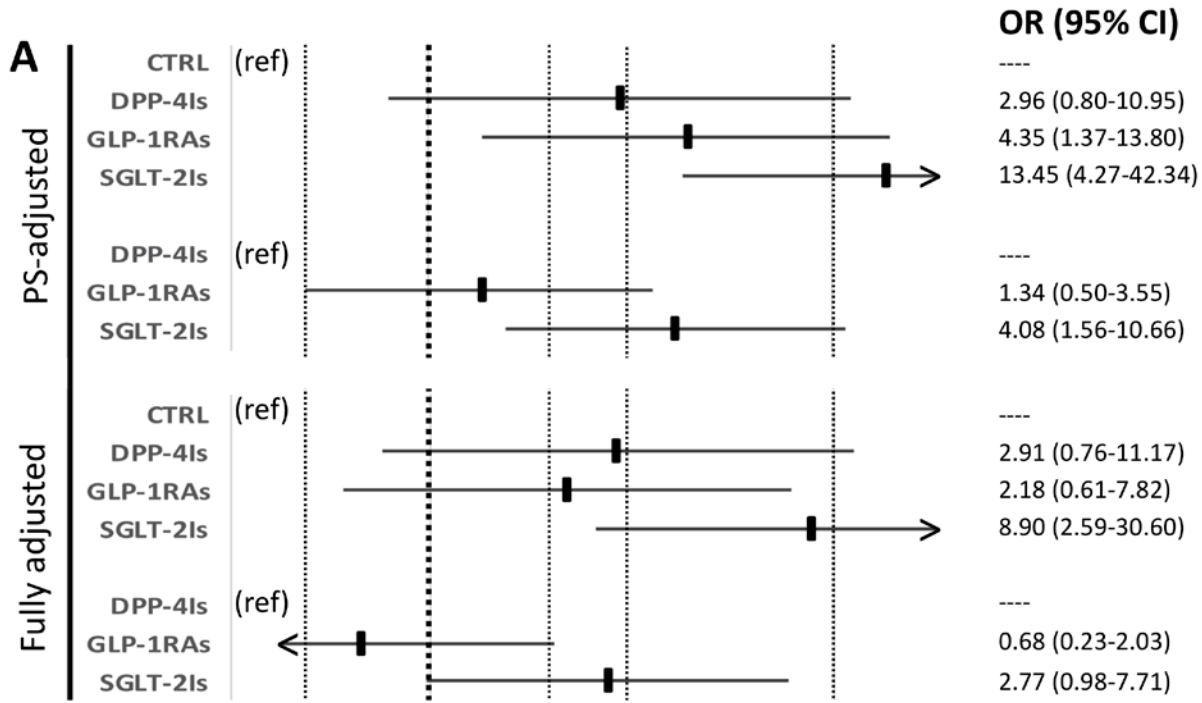
When evaluating the effects of treatment if taken as intended[2], people who continued treatment with sc semaglutide 2.4 mg achieved an additional mean weight loss of 8.8% whereas people on placebo regained 6.5%. The treatment difference was statistically significant. People who stayed on sc semaglutide 2.4 mg for 68 weeks achieved a weight loss of 18.2%.

NOVO company announcement

Fatty Liver Index

Modificazioni nel passaggio ai nuovi farmaci antidiabetici

12-month results



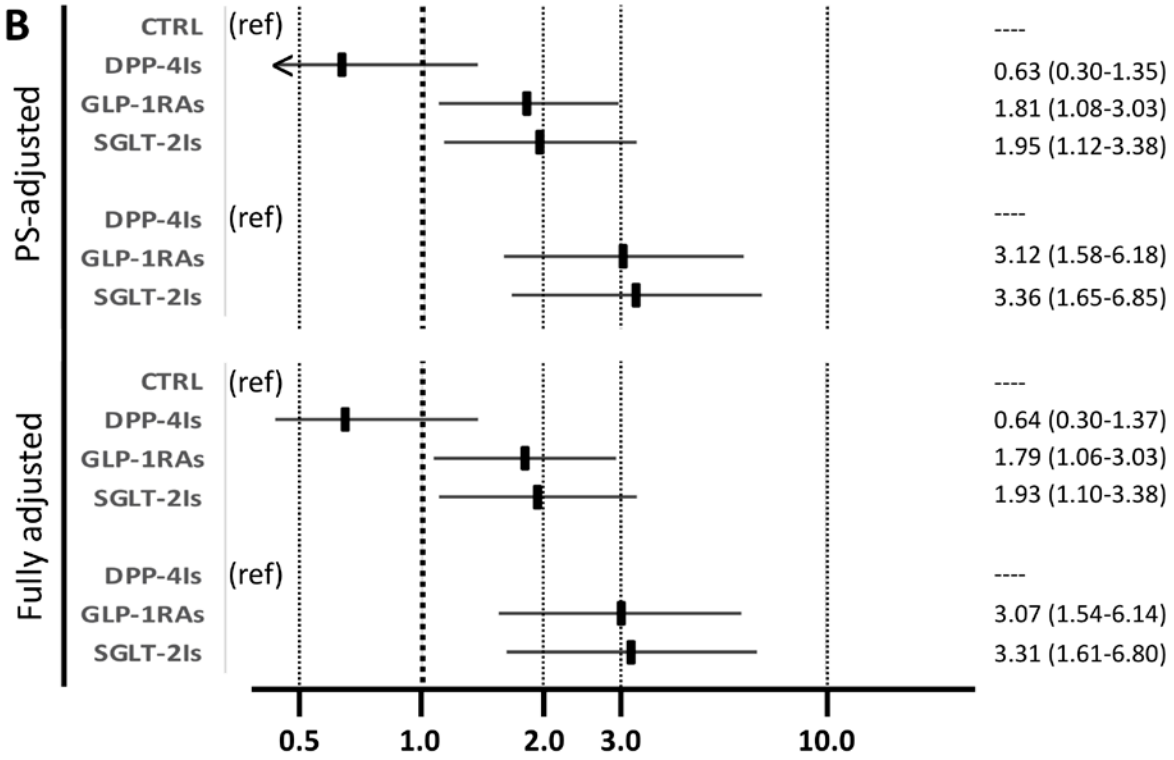
637 pazienti con DM2 passati da metformina con/senza sulfoniluree e/o pioglitazone treatment ai nuovi farmaci (**GLP-1RA, DPP-4I,SGLT-2**).

165 pazienti mantenuti con la terapia originale utilizzati come controlli.

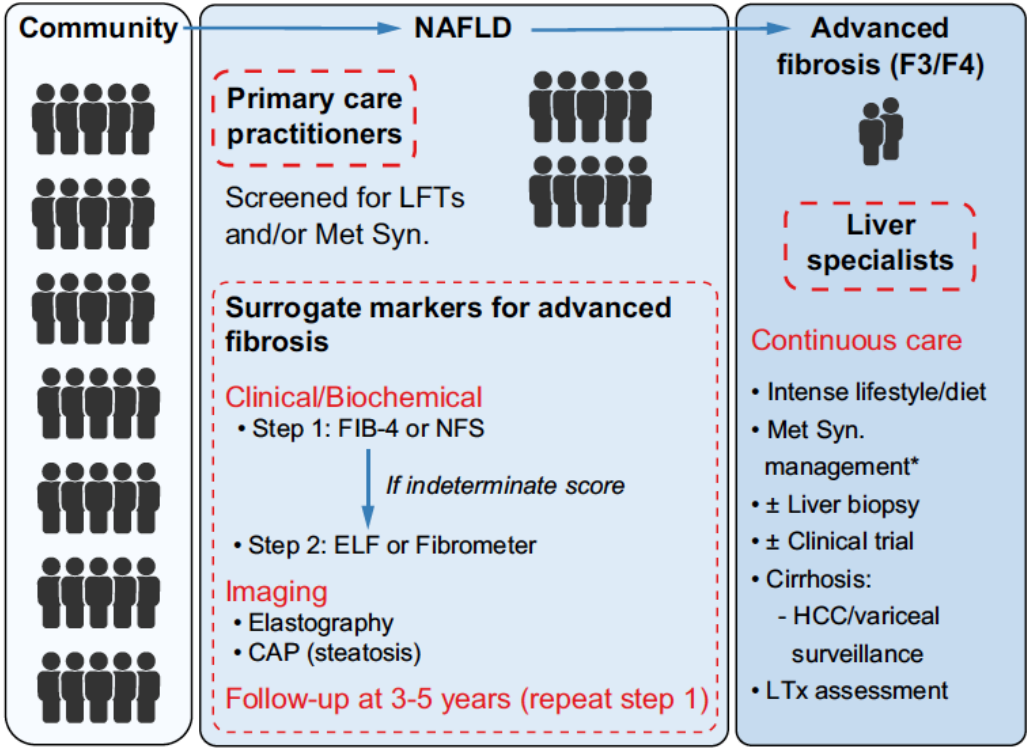
Outcomes: modificazioni del Fatty Liver Index (FLI) e del Fibrosis-4 score (FIB-4)

Fibrosis-4 score

Modificazioni nel passaggio ai nuovi farmaci antidiabetici



Il ruolo del diabetologo nei pazienti con NAFLD



Population with T2DM

- Diabetologists should screen all their patients at regular intervals (≤ 2 years) for advanced fibrosis (NAFLD fibrosis score or FIB-4 w/wo ultrasonography) and refer cases with suspected advanced fibrosis to Liver Units for elastography and eventually liver biopsy.
- Treatment for T2DM should include metformin (up to Child B severity) and anti-diabetic drugs favoring weight loss and liver fat removal, potentially able to reduce fibrosis, and protective for CV and HF risk.
- The use of PIO should be considered in young patients at low CV risk.

Armstrong & Marchesini, J Hepatol 2019