Università degli Studi di Modena e Reggio Emilia

Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze
Dipartimento Integrato di Medicina, Endocrinologia,
Metabolismo e Geriatria

Marco Bertolotti, Chiara Mussi

Steatosi Epatica e Dismetabolismi nell'Anziano

Fra Patologia e Normalità

Napoli, 2 Dicembre 2016

Steatosi Epatica e Dismetabolismi nell'Anziano Fra Patologia e Normalità

Potenziali conflitti di interesse collegati alla presente relazione:

Nessuno

Steatosi Epatica e Dismetabolismi nell'Anziano

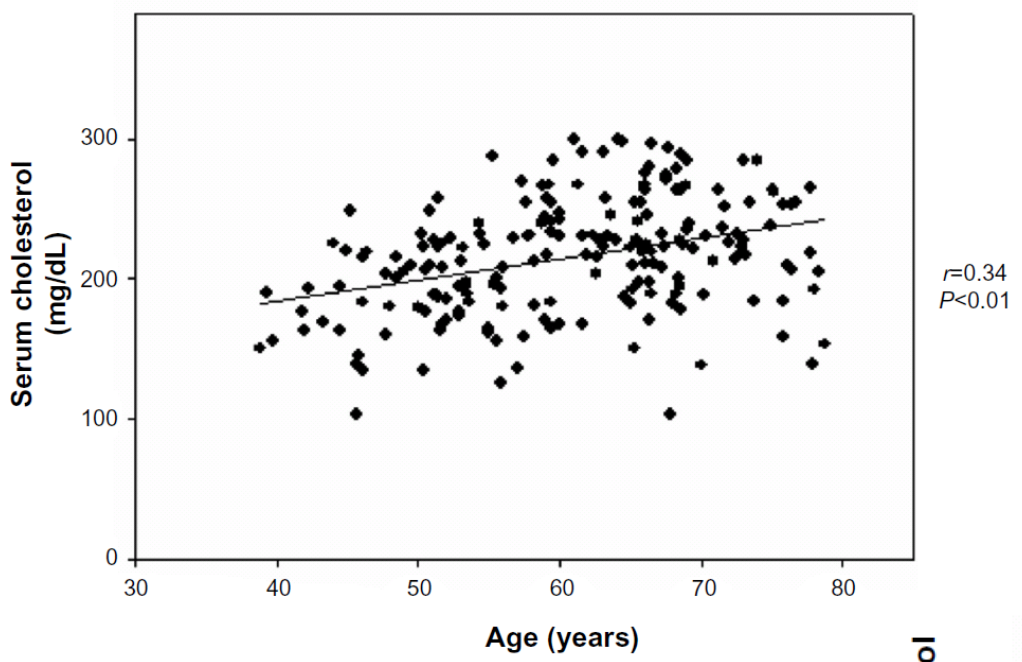
Alterazioni metaboliche associate all'invecchiamento

L'epatopatia steatosica non-alcoolica (NAFLD) nell'anziano

- Fattori ormonali
- Alterazioni meccanismi cellulari
- Rapporto con sindromi geriatriche
- Cenni di terapia

Age-associated alterations in cholesterol homeostasis: evidence from a cross-sectional study in a Northern Italy population

Clinical Interventions in Aging 2014:9 425–432



La colesterolemia aumenta con l'età

La sintesi di colesterolo tende a diminuire con l'età

Marco Bertolotti[1]
Chiara Mussi[1]
Elisa Pellegrini[1]
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Marina Del Puppo[2]
Silvia Ognibene[1]
Lucia Carulli[1]
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Enrica Baldelli[1]
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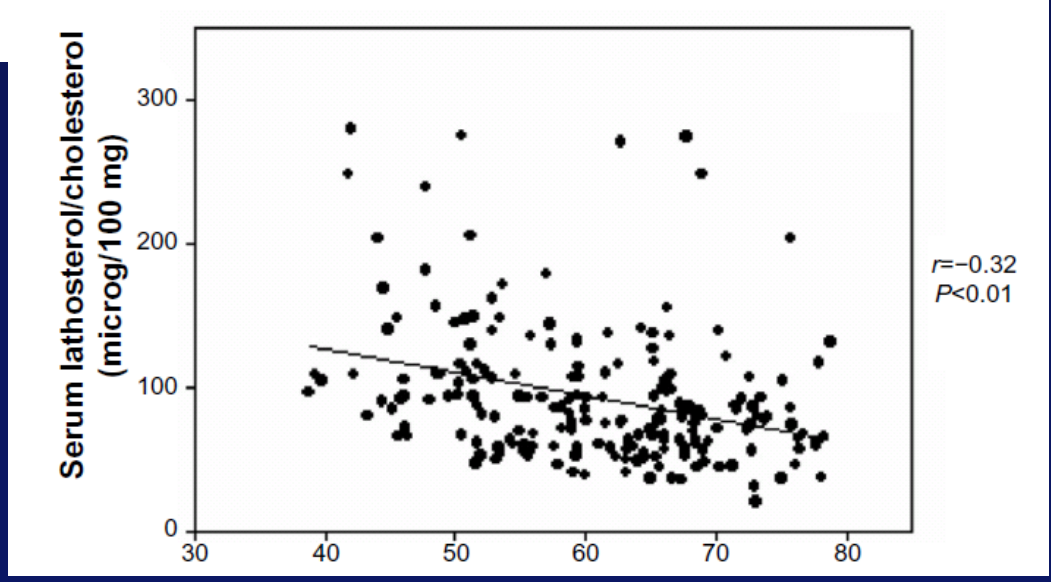
Nicola Carulli[1]



Advancing age and insulin resistance: new facts about an ancient history

G. Paolisso, M. R. Tagliamonte, M. R. Rizzo and D. Giugliano

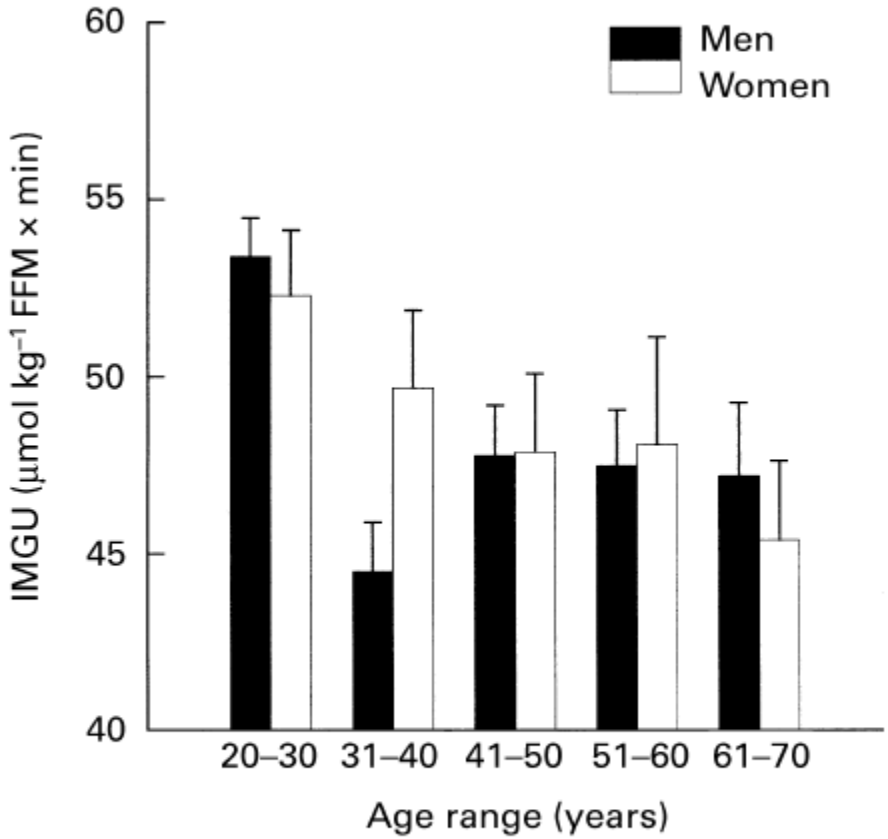


Figure 1 Insulin-mediated glucose uptake (IMGU) in men and women categorized by age. Data are derived from the European Group of Insulin Resistance (EGIR) database.

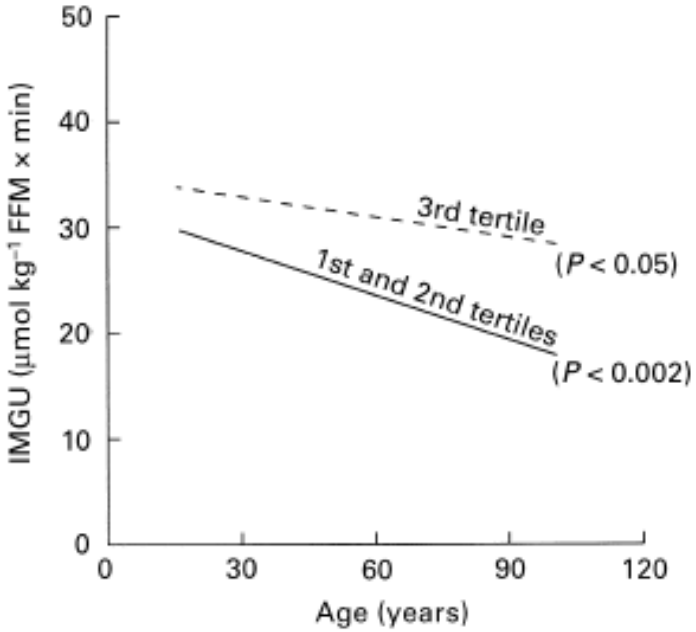


Figure 2 Correlations between insulin-mediated glucose uptake (IMGU) and age in subjects at the third tertile of plasma age- and sex-adjusted dehydroepiandrosterone sulphate (DHEAS) (- - - - - -) ($r = -0{\cdot}38$, $P < 0{\cdot}05$; $n = 25$) and subjects at first and second tertiles of plasma age- and sex-adjusted DHEAS (————) ($r = -0{\cdot}43$, $P < 0{\cdot}002$; $n = 50$). The difference between the two regression lines was also significant ($P < 0{\cdot}03$). (Reproduced from Ref. 36 with the permission of the authors and copyright holder).

European Journal of Clinical Investigation (1999) **29**, 758–769

Riduzione dei livelli di IGF nell'invecchiamento

The Insulin-Like Growth Factor Axis and Plasma Lipid Levels in the Elderly*

GIAN PAOLO CEDA, ELISABETTA DALL'AGLIO, ANDREA MAGNACAVALLO, NICOLA VARGAS, VITTORIO FONTANA, MARCELLO MAGGIO, GIORGIO VALENTI, PHILLIP D. K. LEE, RAYMOND L. HINTZ, AND ANDREW R. HOFFMAN

TABLE 2. Linear regression coefficients (r) and *P* values between age, BMI, and the other measured variables

Variable	Age		BMI	
	r	*P*	r	*P*
IGF-I	−0.37	0.0001	0.01	NS
IGF-II	−0.39	0.0001	0.04	NS
IGFBP-3	−0.53	0.0001	0.05	NS
BMI	−0.29	0.0007		
Chol.	−0.25	0.0037	0.18	0.0463
TG	−0.07	NS	0.28	0.0013
HDL	−0.27	0.0017	−0.19	0.0267
LDL	−0.15	NS	0.18	0.0382
ApoA1	−0.243	0.005	−0.09	NS
ApoB	−0.13	NS	0.19	0.0324

(*J Clin Endocrinol Metab* **83:** 499–502, 1998)

Age-related changes in bile acid synthesis and hepatic nuclear receptor expression

M. Bertolotti*, C. Gabbi*, C. Anzivino*, M. Crestani†, N. Mitro†, M. Del Puppo‡, C. Godio†, E. De Fabiani†, D. Macchioni*, L. Carulli*, A. Rossi*, M. Ricchi*, P. Loria* and N. Carulli*

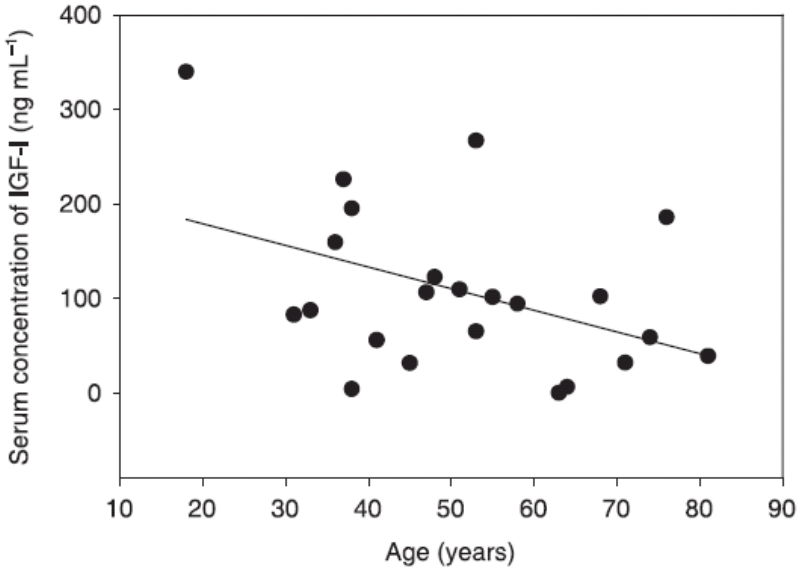
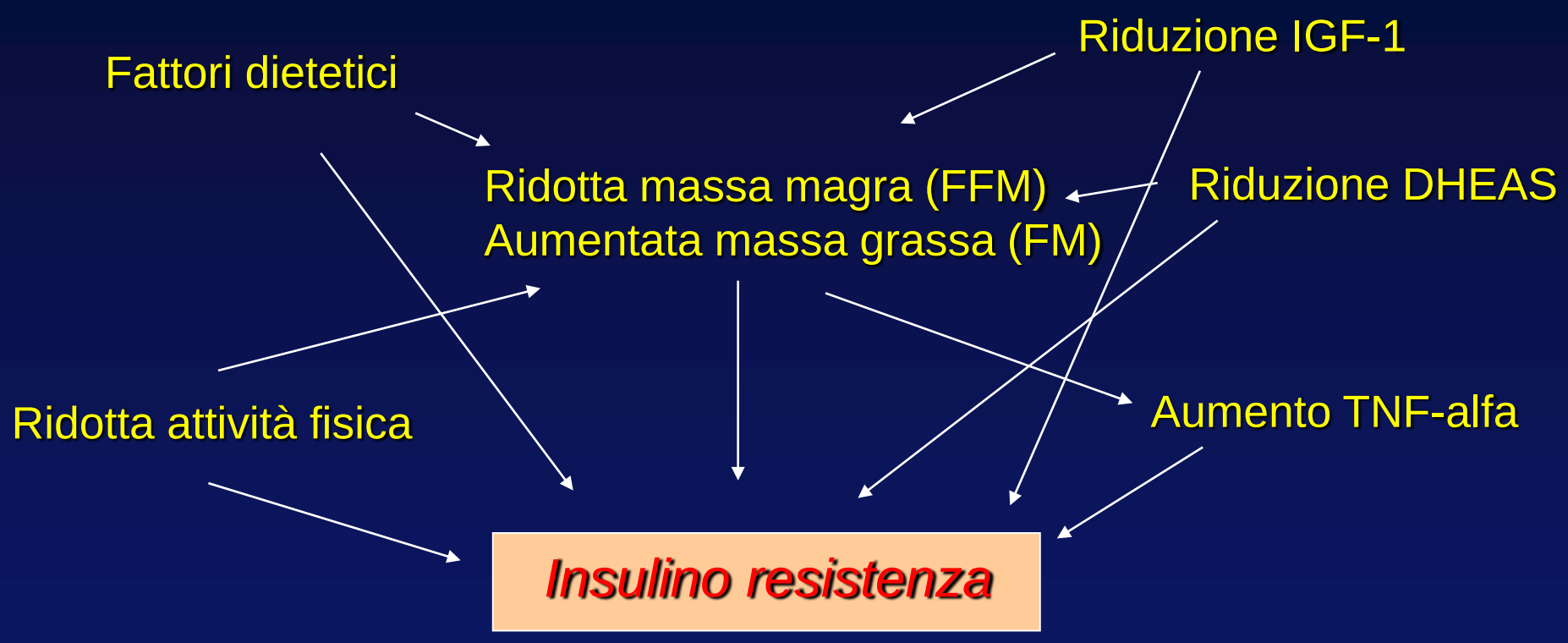


Figure 4 Correlation between age and serum levels of IGF-I in the population investigated ($n = 23$). Serum hormone levels were analysed by chemiluminescence analysis. Linear regression analysis was performed by the least square method. Age vs. IGF-I: $r = -0{\cdot}43$, $P < 0{\cdot}05$.

European Journal of Clinical Investigation (2007) **37**, 501–508

Insulino-resistenza nell'anziano

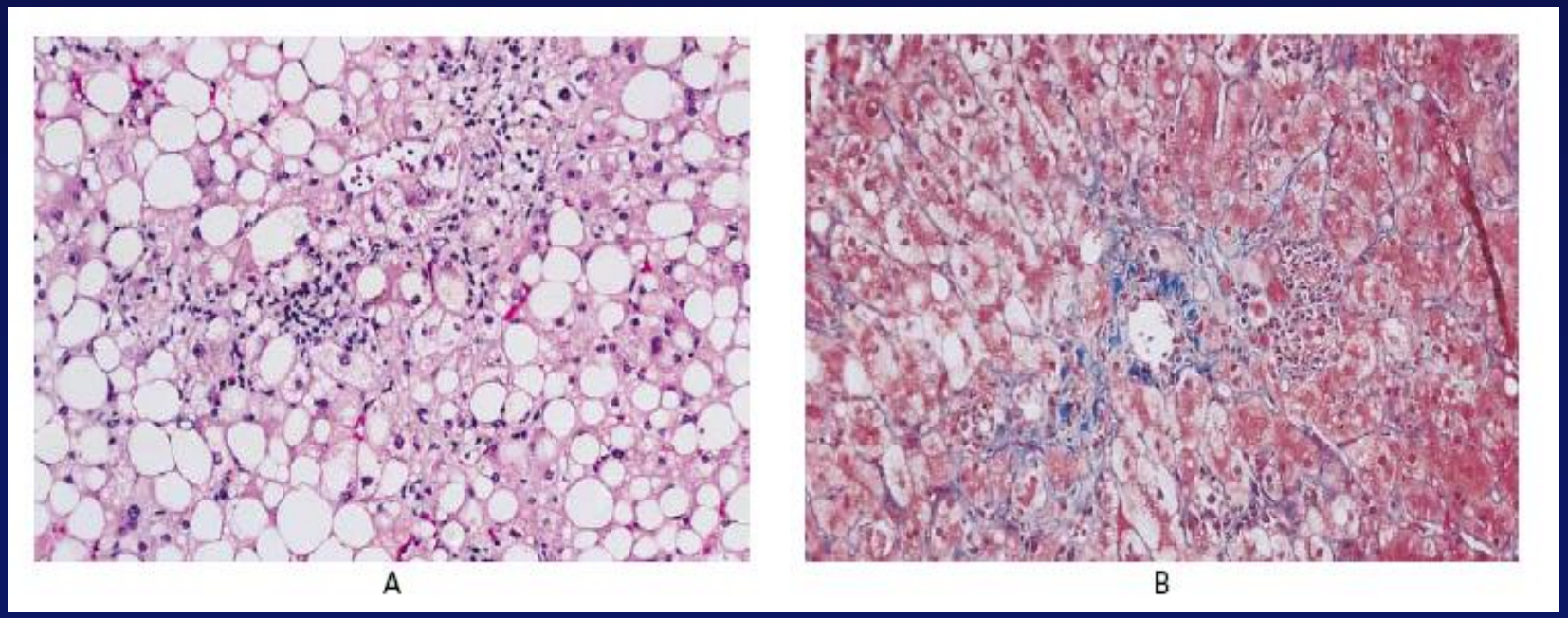


European Journal of Clinical Investigation (1999) **29**, 758–769

Epatopatia Steatosica Non-Alcoolica
(Non-Alcoholic Fatty Liver Disease)
Steatoepatite Non-Alcolica
(Non-Alcoholic Steato- Hepatitis)

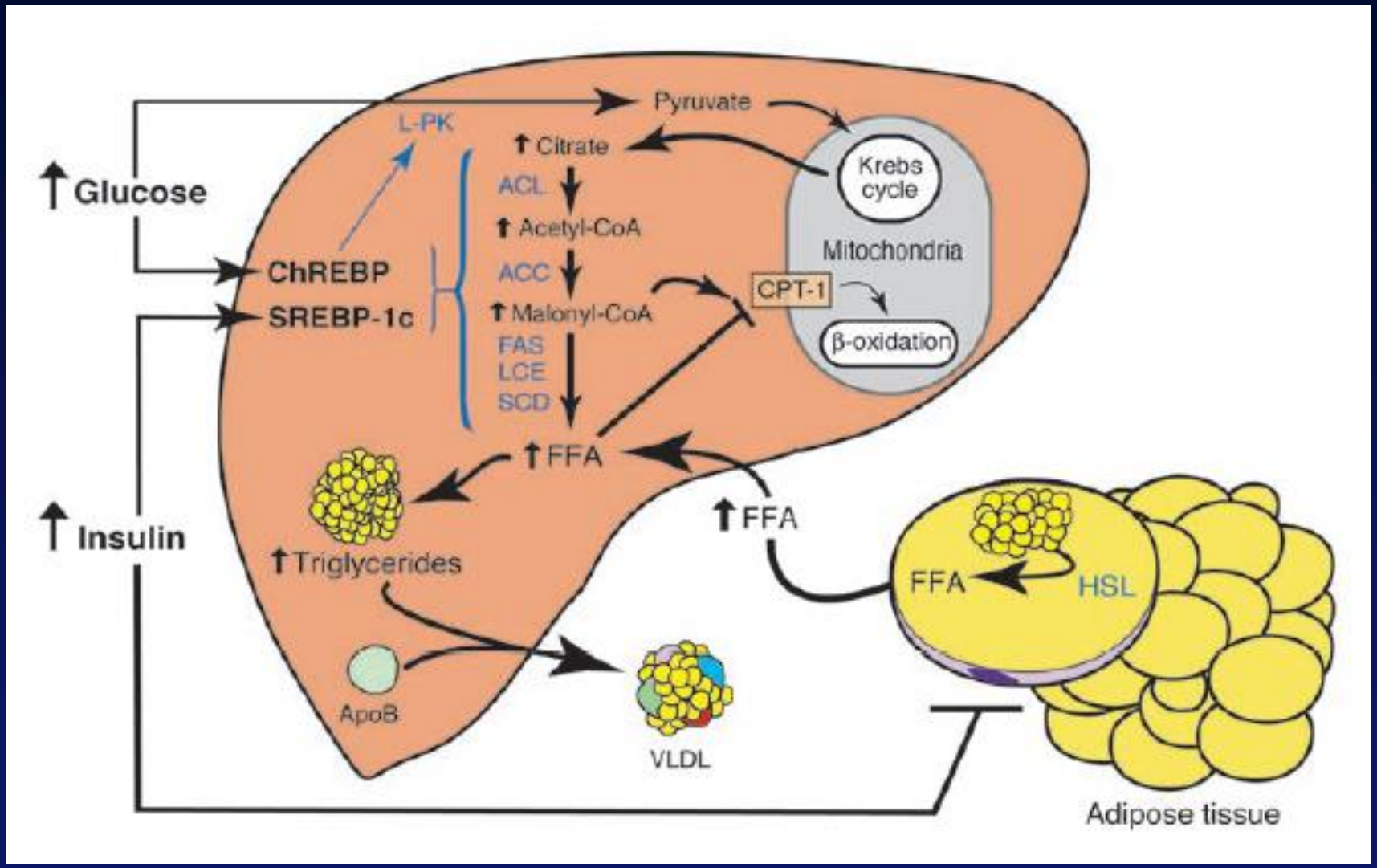
Definizione:

Espressione di danno istologico epatico simile a quello osservato nell'epatopatia steatosica alcoolica in assenza di significativo introito etilico



Angulo, NEJM 2002; 346: 1221-1231

NAFLD e Insulino-Resistenza



Browning and Horton, JCI 2004; 114: 147-152

TABLE 2
Univariate and multivariate logistic regression analyses of factors associated with incident CVD events among type 2 diabetic patients

Variables	Univariate	Multivariate model 1	Multivariate model 2	Multivariate model 3
NAFLD				
OR	1.91	1.9	1.84	1.53
95% CI	1.4–2.2	1.4–2.2	1.4–2.1	1.1–1.7
P values	0.001	0.001	0.001	0.02
ATP III–defined metabolic syndrome				
OR	1.64	1.64	1.62	1.58
95% CI	1.3–2.5	1.3–2.3	1.3–2.1	1.3–2
P values	0.001	0.001	0.001	0.01
Age				
OR	1.14	1.13	1.13	1.12
95% CI	1.07–1.16	1.07–1.14	1.07–1.14	1.06–1.14
P values	0.001	0.001	0.001	0.001
Sex				
OR	1.50	1.48	1.46	1.46
95% CI	1.2–2	1.2–2	1.2–1.9	1.2–1.9
P values	0.001	0.001	0.001	0.001
Diabetes duration				
OR	1.08	NS	NS	NS
95% CI	0.8–1.3	NS	NS	NS
P values	NS	NS	NS	NS
A1C				
OR	1.51	1.46	NS	NS
95% CI	1.1–4.9	1.02–4.2	NS	NS
P values	0.02	0.05	NS	NS
Smoking status				
OR	1.44	1.42	1.40	1.40
95% CI	1.1–2.0	1.1–2.0	1.1–1.9	1.1–1.9
P values	0.01	0.01	0.01	0.01
LDL cholesterol				
OR	1.18	NS	NS	NS
95% CI	0.9–1.4	NS	NS	NS
P values	NS	NS	NS	NS
GGT				
OR	1.42	1.40	1.27	NS
95% CI	1.1–2.0	1.1–1.9	1.05–1.7	NS
P values	0.001	0.001	0.01	NS
Use of medications				
OR	1.0	NS	NS	NS
95% CI	0.7–1.2	NS	NS	NS
P values	NS	NS	NS	NS

NAFLD Rischio Cardiovascolare in DM tipo 2

Targher et al,
Diabetes 2005; 54: 3541-3546

NAFLD e IMT

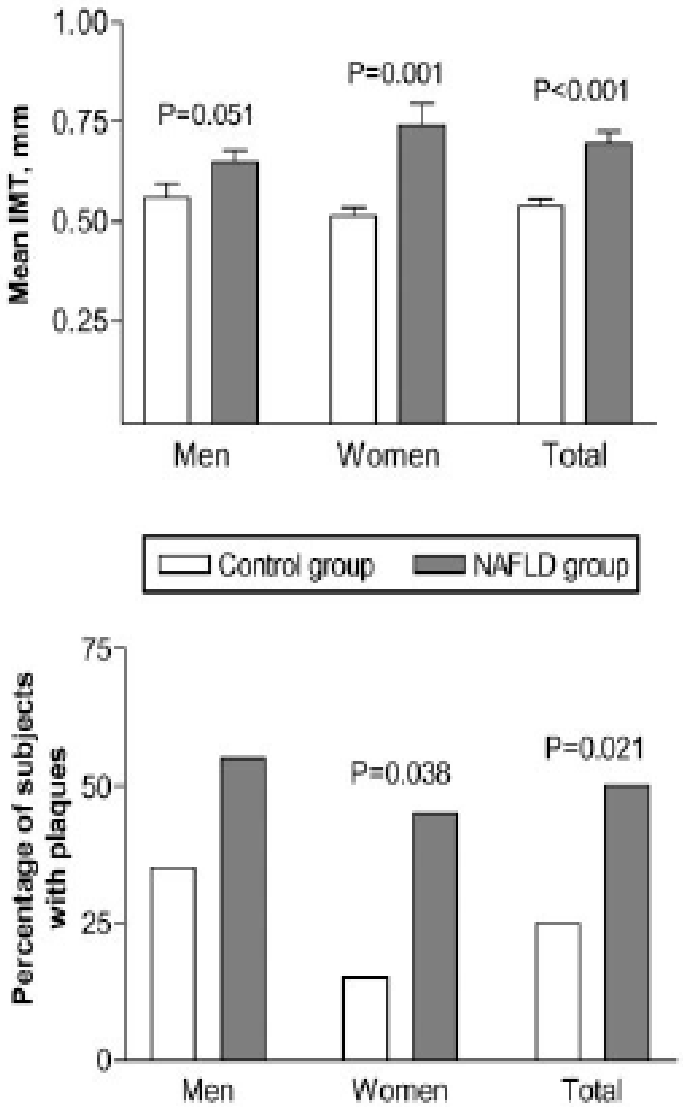


Figure 1. Comparisons of mean carotid IMT (top) and plaque frequency (bottom) in patients with NAFLD and control subjects. Error bars represent SEM.

Table 1 Ultrasonographic carotid findings in subjects with or without fatty liver of unspecified etiology

Carotid findings	Fatty liver: Absent *n* (%)	Fatty liver: Present *n* (%)	*P*
Normal	19 (7.3)	39 (20.6)	
IMT	27 (10.4)	45 (23.8)	
Plaques	214 (82.3)	105 (55.6)	$P = 4.65 \times 10^{-10}$

Lonardo et al,
World J Gastroenterol 2006; 12: 5826-5833

Brea et al, ATVB 2005; 25: 1045-1050

Ovarian senescence increases liver fibrosis in humans and zebrafish with steatosis

Elena Turola[1,*], Salvatore Petta[2,*], Ester Vanni[3], Fabiola Milosa[1], Luca Valenti[4], Rosina Critelli[1], Luca Miele[5], Livia Maccio[6], Vincenza Calvaruso[2], Anna L. Fracanzani[4], Marcello Bianchini[1], Nazarena Raos[1], Elisabetta Bugianesi[3], Serena Mercorella[1], Marisa Di Giovanni[6], Antonio Craxì[2], Silvia Fargion[4], Antonio Grieco[5], Calogero Cammà[2], Franco Cotelli[7] and Erica Villa[1,‡]

Table 2. Univariate and multivariate analysis of factors associated with significant liver fibrosis (F2-F4) in females with NAFLD

	F0-F1 fibrosis (*n*=111)	F2-F4 fibrosis (*n*=133)	Univariate analysis *P*-value	Multivariate analysis OR (95% CI)	Multivariate analysis *P*-value	Variance inflation factor
Mean age* (years)	51.8±10.5	52.1±12.5	0.82	0.977 (0.940-1.015)	0.23	2.76
Mean body mass index (kg/m^2)	28.5±5.9	30.5±5.3	0.004	1.045 (0.987-1.106)	0.12	1.07
Waist circumference (cm)	100.1±13.5	99.6±13.3	0.81			
Alanine aminotransferase (IU/l)	56.9±35.6	84.1±65.6	0.001			
Cholesterol (mg/dl)	217.2±45.8	211.5±46.0	0.33			
HDL cholesterol (mg/dl)	60.7±20.2	54.7±15.6	0.009	0.982 (0.964-1.000)	0.04	1.19
Triglycerides (mg/dl)	129.3±62.5	146.7±77.0	0.05	1.001 (0.996-1.005)	0.78	1.20
Blood glucose (mg/dl)	102.8±34.0	107.8±36.1	0.27			
Insulin (μU/ml)	14.7±9.2	21.7±13.8	<0.001			
HOMA	3.76±2.53	5.34±3.57	<0.001			
Type 2 diabetes	20	43	0.01	1.914 (0.965-3.794)	0.06	1.12
Arterial hypertension	42	56	0.54			
Menopause	72	98	0.13	2.717 (1.020-7.237)	0.04	2.77
Steatosis grade 1 vs 2-3	64, 47	39, 94	<0.001			
Lobular inflammation 0-1 vs 2-3	99, 12	71, 62	<0.001			
Ballooning 0, 1, 2	42, 42, 27	25, 46, 62	<0.001			
NASH (yes, no)	48, 63	25, 108	<0.001	3.214 (1.743-5.926)	<0.001	1.05

Data are given as mean±standard deviation or as number of case. *Age forced into the model owing to the strong relation with menopause.

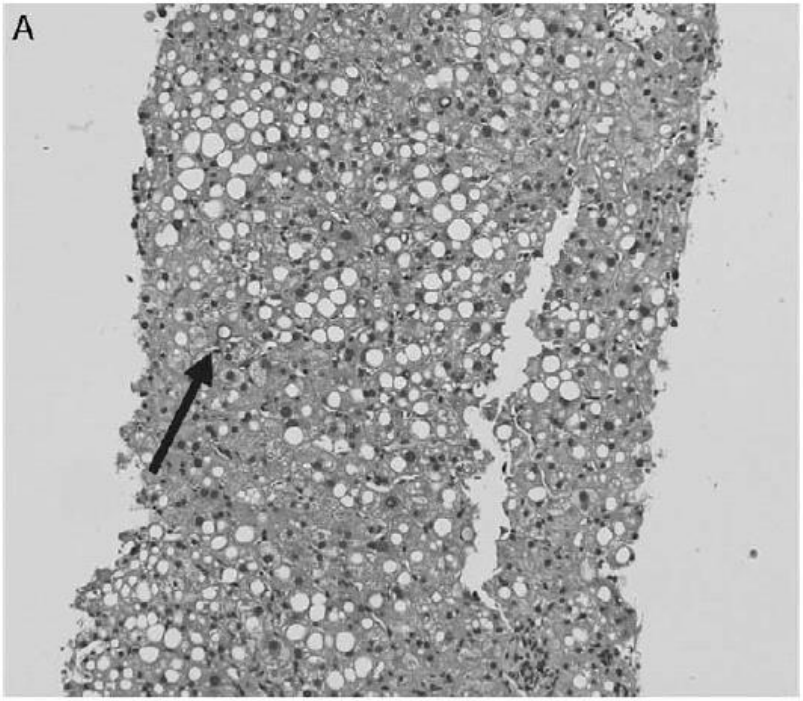
© 2015. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2015) 8, 1037-1046 doi:10.1242/dmm.019950

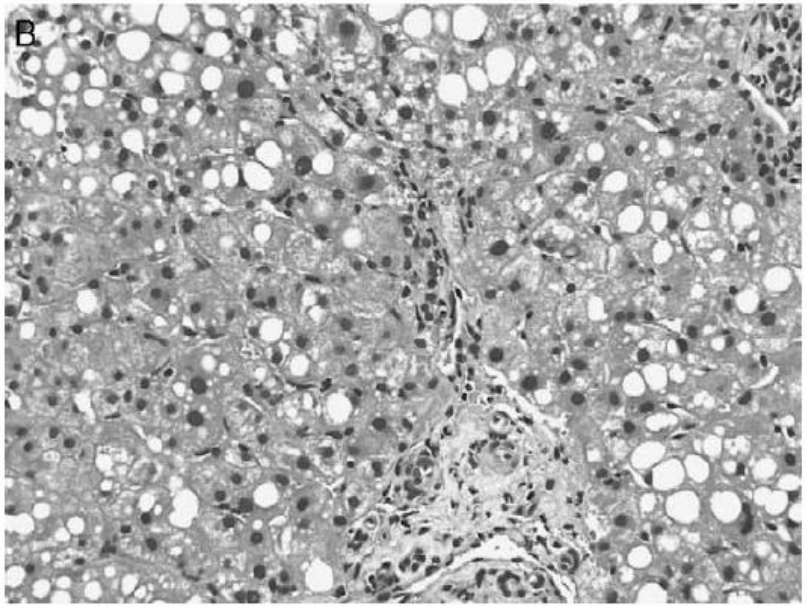
Nonalcoholic Fatty Liver Disease Induced by Leuprorelin Acetate

Chiara Gabbi, MD, Francesca Carubbi, MD,* Luisa Losi, MD,† Paola Loria, MD,* Matteo Costantini, MD,† Marco Bertolotti, MD,* and Nicola Carulli, MD**

Abstract: Leuprorelin acetate is an agonist of gonadotropin-releasing hormone, used as a first choice treatment in patients with prostate carcinoma. The impact of leuprorelin therapy in liver function and metabolism is largely unknown. We report about a patient who had been treated for 32 months with leuprorelin acetate, who developed a nonalcoholic fatty liver disease (NAFLD), associated with a focal lesion at the IV hepatic segment where histologic features appeared to be more severe. The patient, in addition to NAFLD, presented a marked iatrogenic hypotestosteronemia and full-criteria meeting the diagnosis of metabolic syndrome, including insulin resistance. The radiologic and clinical findings, the histopathologic features, and the absence of any hepatic abnormalities before treatment, support a causal role of leuprorelin in inducing metabolic derangement that, most likely secondary to androgen-deprivation, were, in turn, responsible for the development of NAFLD. In conclusion, this is the first case report of NAFLD with focal fatty liver associated with leuprorelin therapy. Patients in leuprorelin should be carefully monitored for the development of liver disease.

(*J Clin Gastroenterol* 2008;42:107–110)





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TOPIC HIGHLIGHT

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

Nonalcoholic fatty liver disease and aging: Epidemiology to management

Marco Bertolotti, Amedeo Lonardo, Chiara Mussi, Enrica Baldelli, Elisa Pellegrini, Stefano Ballestri, Dante Romagnoli, Paola Loria

Core tip: Nonalcoholic fatty liver disease (NAFLD) is a common disease in the elderly, in whom it follows a more severe course due to worse hepatic and extrahepatic manifestations. The former include nonalcoholic steatohepatitis and hepatocellular carcinoma; the latter include cardiovascular and metabolic complications. The pathophysiology, diagnosis and principles of treatment that are specifically relevant to elderly patients with NAFLD are critically revised here. Based on these findings, we conclude that a more accurate understanding of the molecular mechanisms of geriatric NAFLD will help in identifying the most appropriate diagnostic and therapeutic approach in the individual elderly patient.

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DOI: 10.3748/wjg.v20.i39.14185

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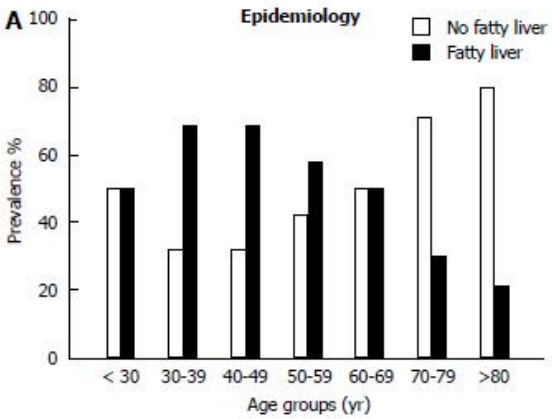
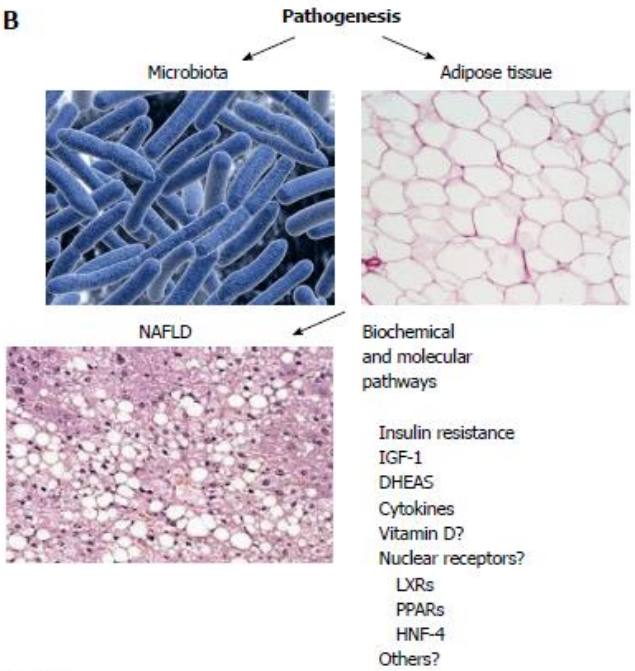
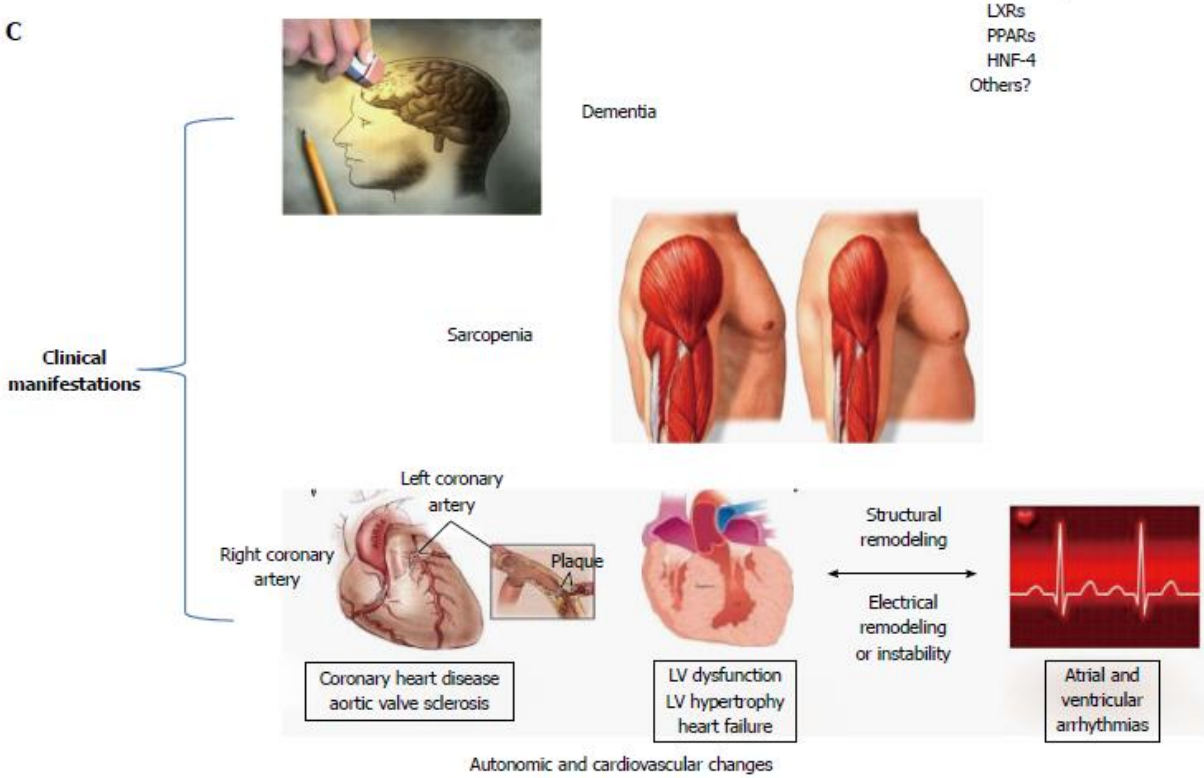
Marco Bertolotti, Amedeo Lonardo, Chiara Mussi, Enrica Baldelli, Elisa Pellegrini, Stefano Ballestri, Dante Romagnoli, Paola Loria

Bertolotti M *et al*. Nonalcoholic fatty liver disease and aging







Arch Intern Med. 2007 October 22; 167(19): 2145–2146. doi:10.1001/archinte.167.19.2145-b.

Insulin Resistance and Cognitive Decline May Be Common Soil for Frailty Syndrome

Angela Marie Abbatecola, MD, **Luigi Ferrucci, PhD**, **Raffaele Marfella, MD**, and **Giuseppe Paolisso, MD**

There is strong evidence showing that normal functioning of the insulin-signaling pathway is crucial for the maintenance of adequate cognitive function.[5] We studied the relationship between IR-HOMA score and global cognitive performance (Mini-Mental State Examination [MMSE]) as well as executive functioning (Trail-Making Test [TMT] times) in 597 older persons with a mean age of 73 years from the InCHIANTI study.[5] After adjusting for multiple confounders including MMSE score, IR-HOMA score was significantly associated with poor visual scanning (TMT-A) (β=11.005; P=.02), poor visual scanning with added cognitive flexibility (TMT-B) (β=28.379; P<.001), and poor cognitive efficiency (difference between TMT-B and TMT-A) (β=17.374; P=.01).[5]

These data support the notion that insulin modulates glucose use in the central nervous system through receptors located in the hippocampus and frontal cortex (which is putatively associated with executive functioning). Given our findings[2,3,5] and those of Barzilay et al,[1] it would be interesting to verify if cognitive decline is associated with increased risk of developing frailty in older nondemented persons and whether such correlation is mediated by IR.

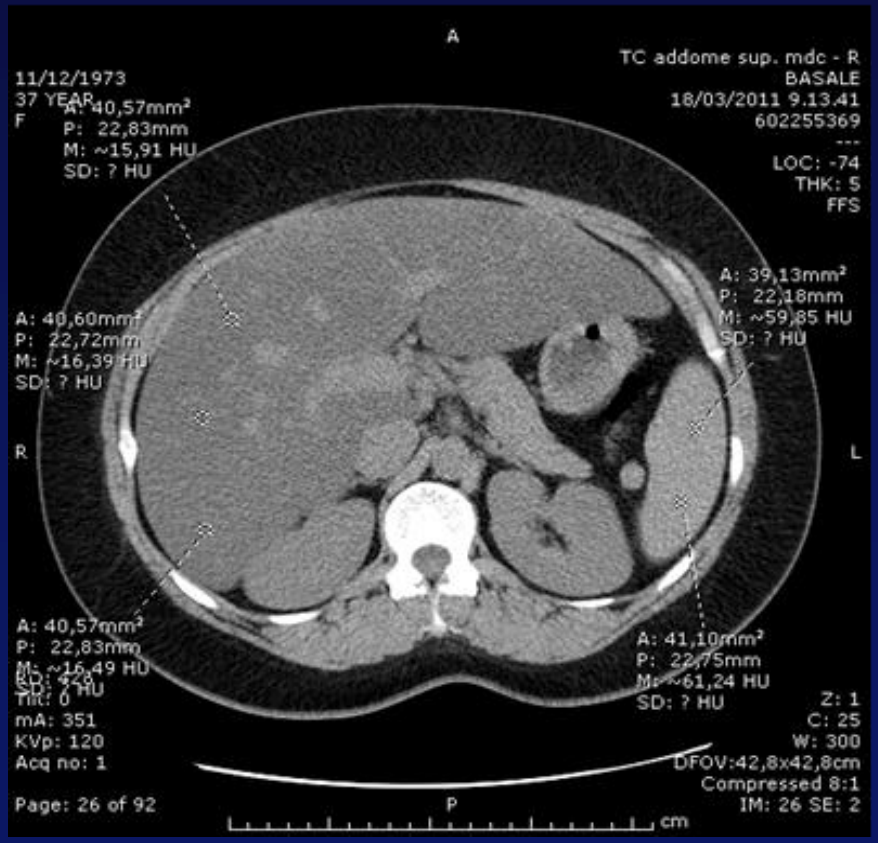
STEATOSI EPATICA, SARCOPENIA E INVECCHIAMENTO

I livelli di densità radiologica TC sono stati rilevati:

- a livello dell'immagine assiale dell'ilo epatico,
- in regioni periferiche del fegato e della milza, lontano da vasi sanguigni,
- considerando regioni di interesse (ROI) di 40 mm^2

Il rapporto tra i due valori densitometrici (L/S ratio), è considerato come indice di accumulo di grasso nel fegato.

Studio delle Immagini TC Fegato



Bertolotti M et al., dati non pubblicati

STEATOSI EPATICA, SARCOPENIA E INVECCHIAMENTO

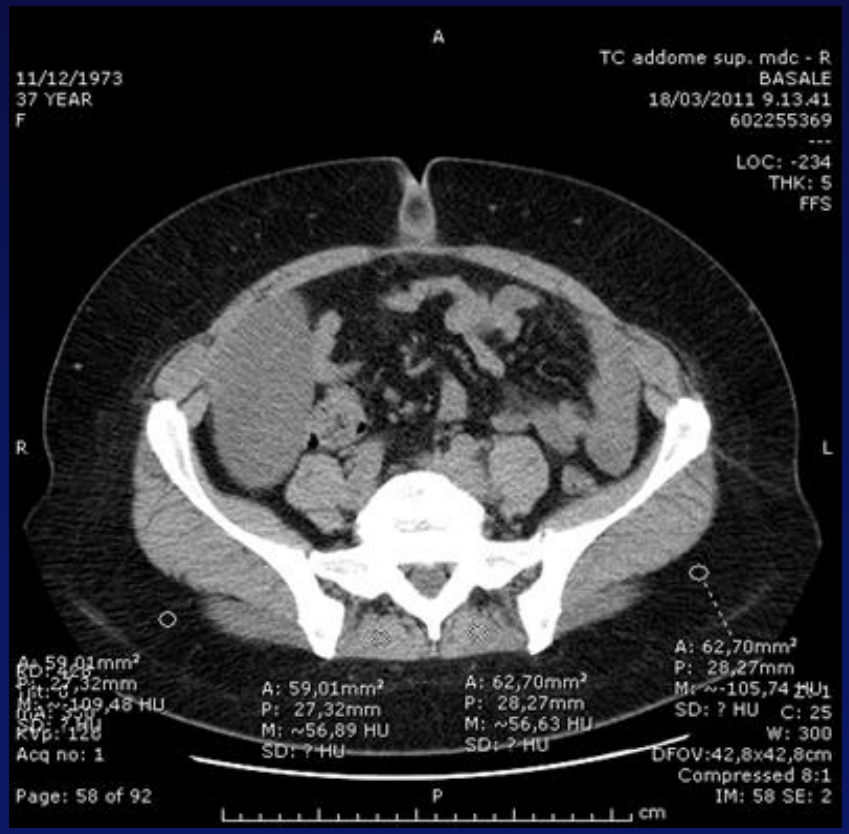
I livelli di densità radiologica TC sono stati rilevati:

- a livello dell'immagine assiale ombelicale,
- Nel muscolo multifido e nel grasso sottocutaneo, lontano da vasi sanguigni,
- considerando regioni di interesse (ROI) di 60 mm^2

Il rapporto tra i due valori densitometrici (MM/F ratio), è considerato come indice di accumulo di grasso nel muscolo scheletrico.

Bertolotti M et al., dati non pubblicati

Studio delle Immagini TC
Muscolo



STEATOSI EPATICA, SARCOPENIA E INVECCHIAMENTO

- Allo scopo di minimizzare l'effetto dell'età, è stata eseguita l'analisi della covarianza con l'età come covariata. Con tale analisi è emerso un dato ai limiti della significatività statistica (P=0,055).
- per approfondire ulteriormente il rapporto fra densitometria epatica e muscolare al netto dell'età è stata condotta un'analisi di correlazione parziale fra le variabili L/S ratio e MM/F ratio, impostando l'età come variabile controllata. E' stata evidenziata la presenza di una correlazione, statisticamente significativa (P < 0,05).

Analisi di correlazione parziale
(Età come variabile controllata)

	r	p
L/S vs MM/F	- 0.13	0.02

Bertolotti M et al., dati non pubblicati

STEATOSI EPATICA, SARCOPENIA E INVECCHIAMENTO

- I risultati del presente studio evidenziano l'importante impatto dell'età su una serie di variabili, sia di tipo clinico che riguardanti il metabolismo dei glucidi e dei lipidi.

- Le analisi eseguite hanno permesso di evidenziare una correlazione significativa, al netto dell'età, fra infiltrazione grassa del fegato e del muscolo, condizioni associate a quadri clinici di frequente riscontro quali, rispettivamente, la steatosi epatica e la sarcopenia

- È plausibile che entrambe le condizioni possano essere influenzate da fattori patogenetici comuni, anche se le due malattie non presentano lo stesso trend di correlazione con l'età, come dimostrato dagli studi epidemiologici, e possono non essere quindi necessariamente presenti negli stessi soggetti.

Myosteatosis and myofibrosis: Relationship with aging, inflammation and insulin resistance

Elena Zoico [a,*], Francesca Corzato [a], Clara Bambace [a], Andrea P. Rossi [a], Rocco Micciolo [b], Saverio Cinti [c], Tamara B. Harris [d], Mauro Zamboni [a]

Table 2
Simple correlations between muscle quality, and anthropometric, body composition variables, intermuscular adipose tissue, adipokines, inflammation and insulin resistance in healthy elderly men ($n = 11$).

	Myofibrosis (r)	Myosteatosis (r)
BMI	0.602*	0.717*
Waist circumference	0.763**	0.713*
Weight	0.497	0.646*
FM[a]	0.662*	0.865***
FM%[a]	0.681*	0.872***
LM[a]	0.123	0.106
App LM[a]	−0.071	−0.124
IMAT[b]	0.620*	0.849***
Paraspinous muscle area[b]	−0.700*	−0.341
Leptin	0.809**	0.864***
Adiponectin	−0.327	−0.336
IL-6	−0.269	−0.187
hs-CRP	0.591*	0.418
Glucose	0.280	0.358
Insulin	0.164	0.436
HOMA index	0.218	0.455

BMI, body mass index; FM, fat mass; LM, lean mass; App LM, appendicular lean mass; IMAT, intermuscular adipose tissue; hs-CRP, high sensitivity C reactive protein; HOMA index, homeostasis model assessment of insulin resistance.

[a] Measured by dual energy X-ray absorptiometry.
[b] Measured by MRI.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

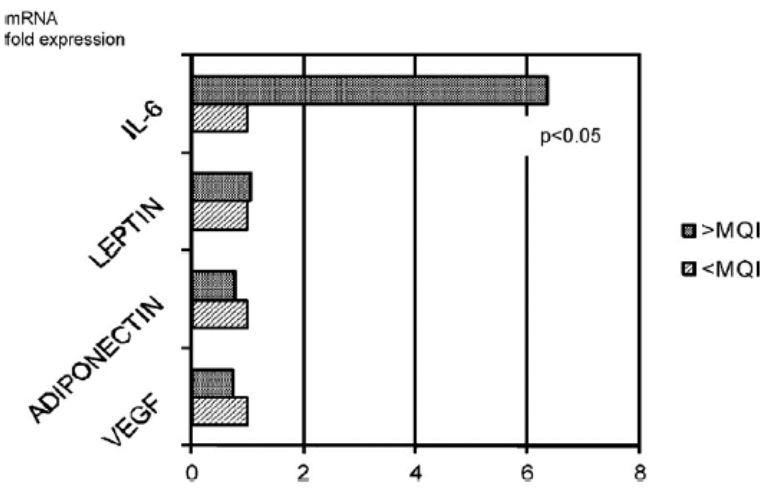


Fig. 2. Comparison between different genes expression in subcutaneous (SAT) biopsies of patient with different degrees of MF and MS, evaluated by MQI.

Archives of Gerontology and Geriatrics 57 (2013) 411–416

Current Pharmaceutical Design, 2013, *19*, 1675-1679

Immune System, Cell Senescence, Aging and Longevity - Inflamm-Aging Reappraised

Stefano Salvioli[1,2], Daniela Monti[3], Catia Lanzarini[1,2], Maria Conte[1,2], Chiara Pirazzini[1,2], Maria Giulia Bacalini[1], Paolo Garagnani[1,2], Cristina Giuliani[1], Elisa Fontanesi[1], Rita Ostan[1], Laura Bucci[1,2], Federica Sevini[1], Stella Lukas Yani[1,2], Annalaura Barbieri[1,2], Laura Lomartire[1,2], Vincenzo Borelli[1,2], Dario Vianello[1], Elena Bellavista[1,2], Morena Martucci[1], Elisa Cevenini[1], Elisa Pini[1,2], Maria Scurti[1], Fiammetta Biondi[1], Aurelia Santoro[1], Miriam Capri[1,2], Claudio Franceschi[1,2,*]

Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases

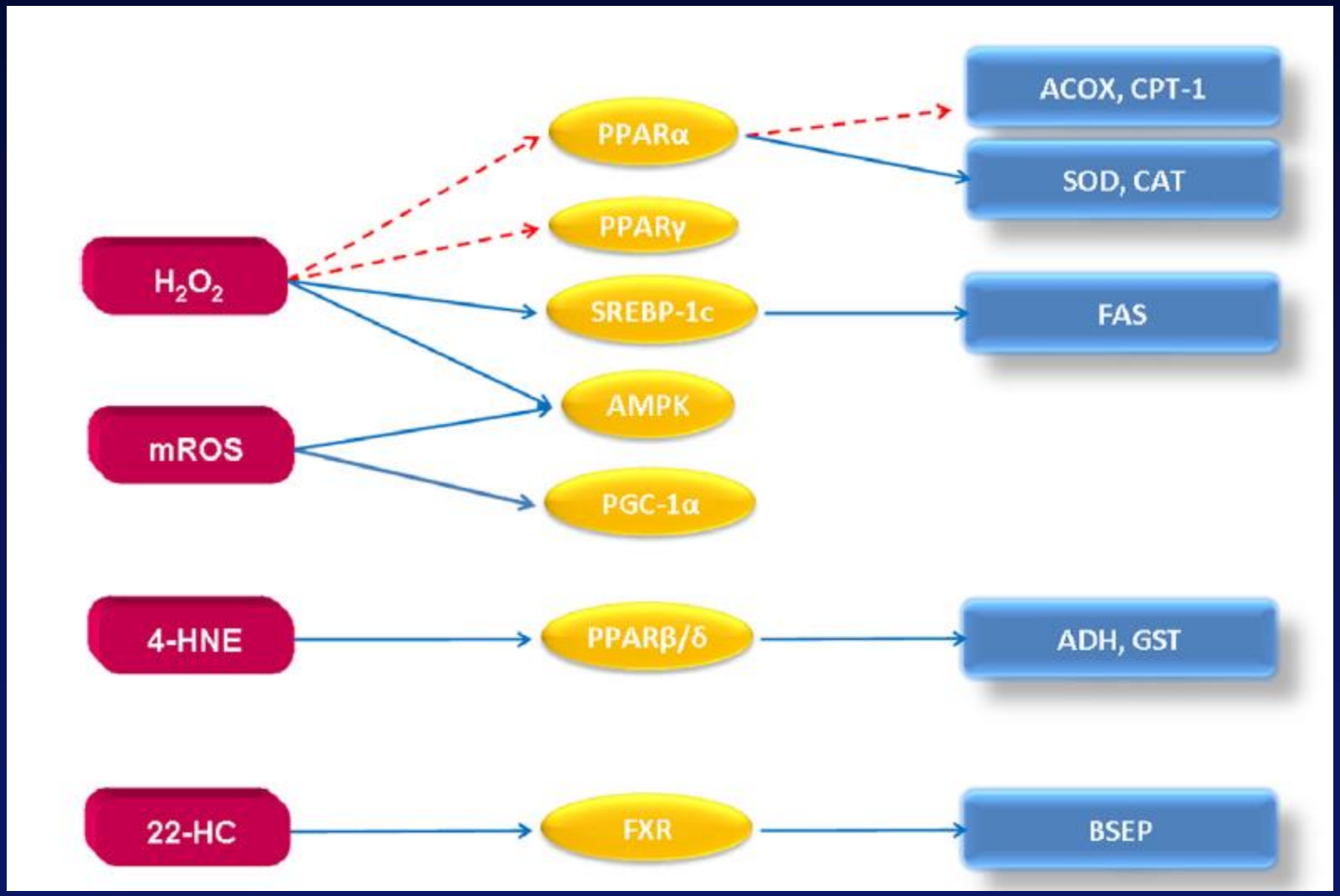
Claudio Franceschi[1,2] and Judith Campisi[3,4]

Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as "inflammaging." Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis. Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people. The session on inflammation of the Advances in Gerosciences meeting held at the National Institutes of Health/National Institute on Aging in Bethesda on October 30 and 31, 2013 was aimed at defining these important unanswered questions about inflammaging. This article reports the main outcomes of this session.

Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 June;69(S1):S4–S9
doi:10.1093/gerona/glu057

Free radical biology for medicine: learning from nonalcoholic fatty liver disease

Gaetano Serviddio*, Francesco Bellanti, Gianluigi Vendemiale

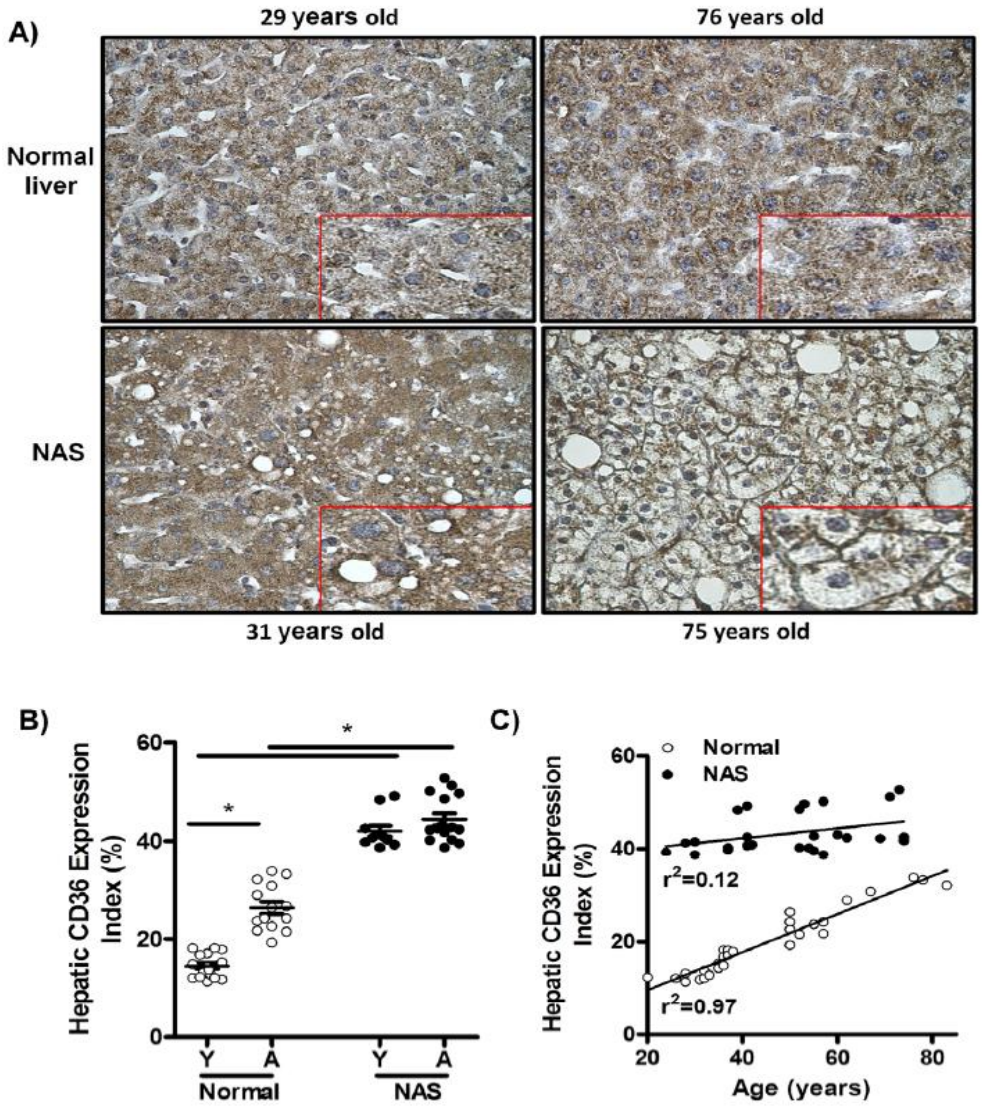


Free Radical Biology and Medicine 65 (2013) 952–968

Increased hepatic CD36 expression with age is associated with enhanced susceptibility to nonalcoholic fatty liver disease

Fareeba Sheedfar[1], Miranda MY Sung[2], Marcela Aparicio-Vergara[1], Niels J Kloosterhuis[1], Maria Eugenia Miquilena-Colina[3], Javier Vargas-Castrillón[3], Maria Febbraio[4], René L Jacobs[5], Alain de Bruin[6], Manlio Vinciguerra[7,8], Carmelo García-Monzón[3], Marten H Hofker[1], Jason RB Dyck[2], and Debby PY Koonen[1]

AGING, April 2014, Vol. 6, No 4



Adipocyte-fatty acid binding protein and non-alcoholic fatty liver disease in the elderly

Marco Masetti · Giampaolo Bianchi · Giordano Gianotti · Marco Giovagnoli · Luca Vizioli · Veronica Zorzi · Valentina Rossi · Paola Forti · Marco Zoli

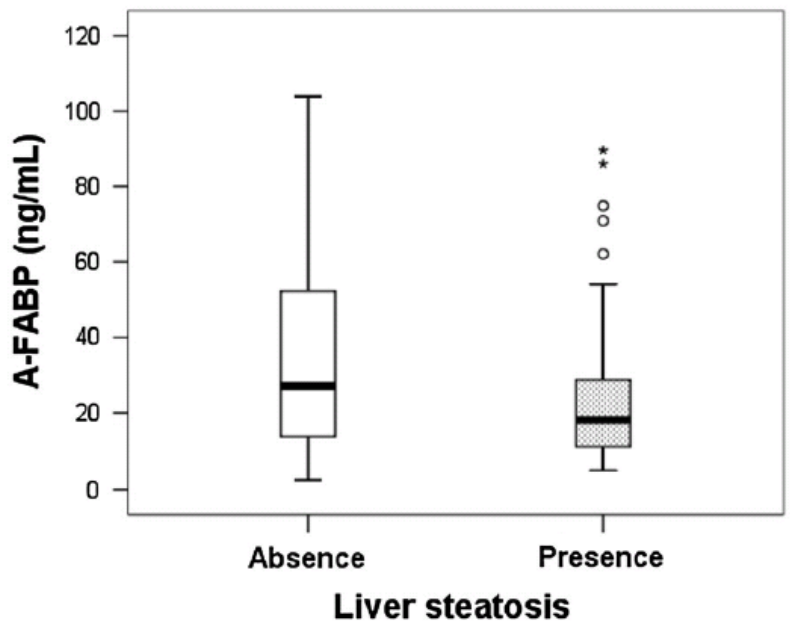


Fig. 1 Serum A-FABP levels in subjects without and with evidence of steatosis at abdominal ultrasound. Data are presented as *box* and *whiskers* plot. $Z = -2.319$, $P = 0.020$

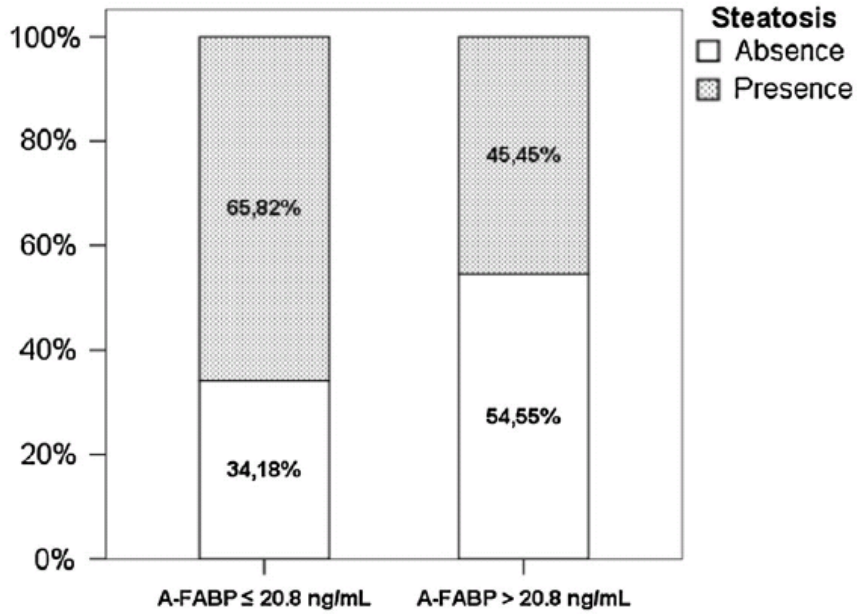


Fig. 2 A-FABP Prevalence of liver steatosis at enrollment in subjects with A-FABP serum levels ≤20.8 ng/mL ($n = 79$) or > 20.9 ng/mL ($n = 77$). Chi-squared (χ^2) = 6.558, $P = 0.010$

Aging Clin Exp Res (2014) 26:241–247

Therapies directed at obesity/metabolic syndrome with potential “liver effects”

- Life style changes directed at obesity and physical fitness
- Bariatric surgery
- Drugs

Courtesy Prof. CP Day

Effect of moderate weight loss on hepatic, pancreatic and visceral lipids in obese subjects

AP Rossi[1], F Fantin[1], GA Zamboni[2], G Mazzali[1], E Zoico[1], C Bambace[1], A Antonioli[1], R Pozzi Mucelli[2] and M Zamboni[1]

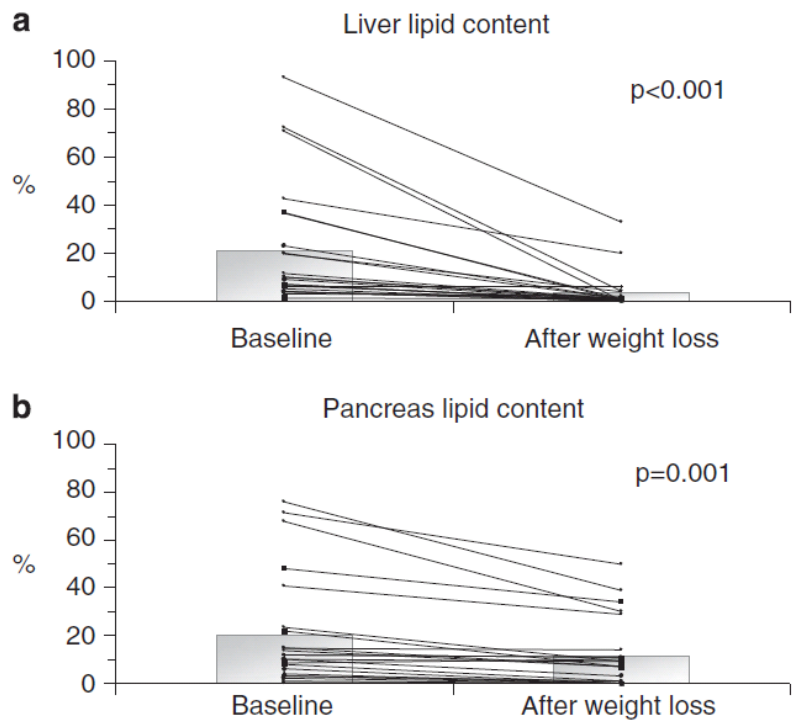


Figure 2. Liver lipid (**a**) and pancreas lipid (**b**) content at baseline and after weight loss.

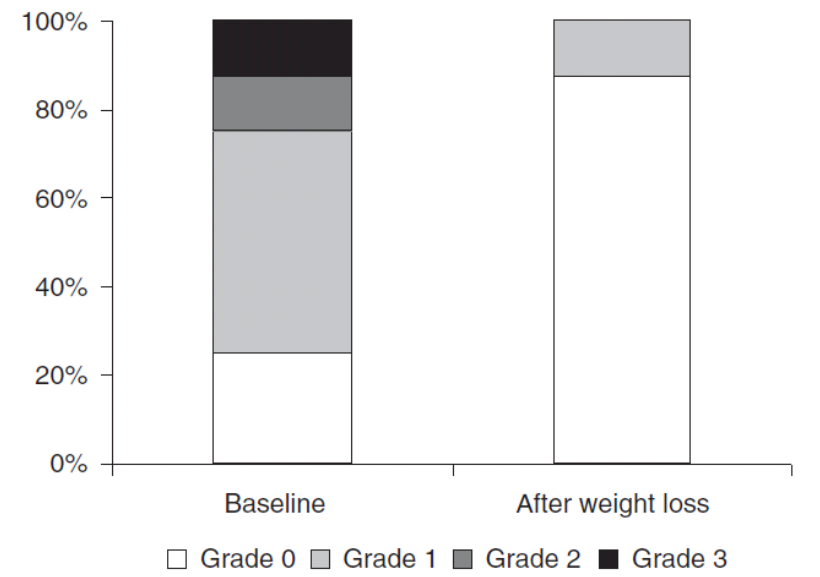


Figure 3. Prevalence of hepatic steatosis before and after weight loss.

Nutrition and Diabetes (2012) **2**, e32; doi:10.1038/nutd.2012.5

OPEN

Long-term lifestyle interventions in middle-aged and elderly men with nonalcoholic fatty liver disease: a randomized controlled trial

Received: 10 August 2016
Accepted: 20 October 2016
Published: 10 November 2016

Fangyuan Dong[1,2,*], Yan Zhang[2,3,*], Yiqin Huang[1,2,3,*], Yiqian Wang[1], Gansheng Zhang[1], Xiaona Hu[1,2], Jiaofeng Wang[2,3], Jie Chen[1,2,3] & Zhijun Bao[1,2,3]

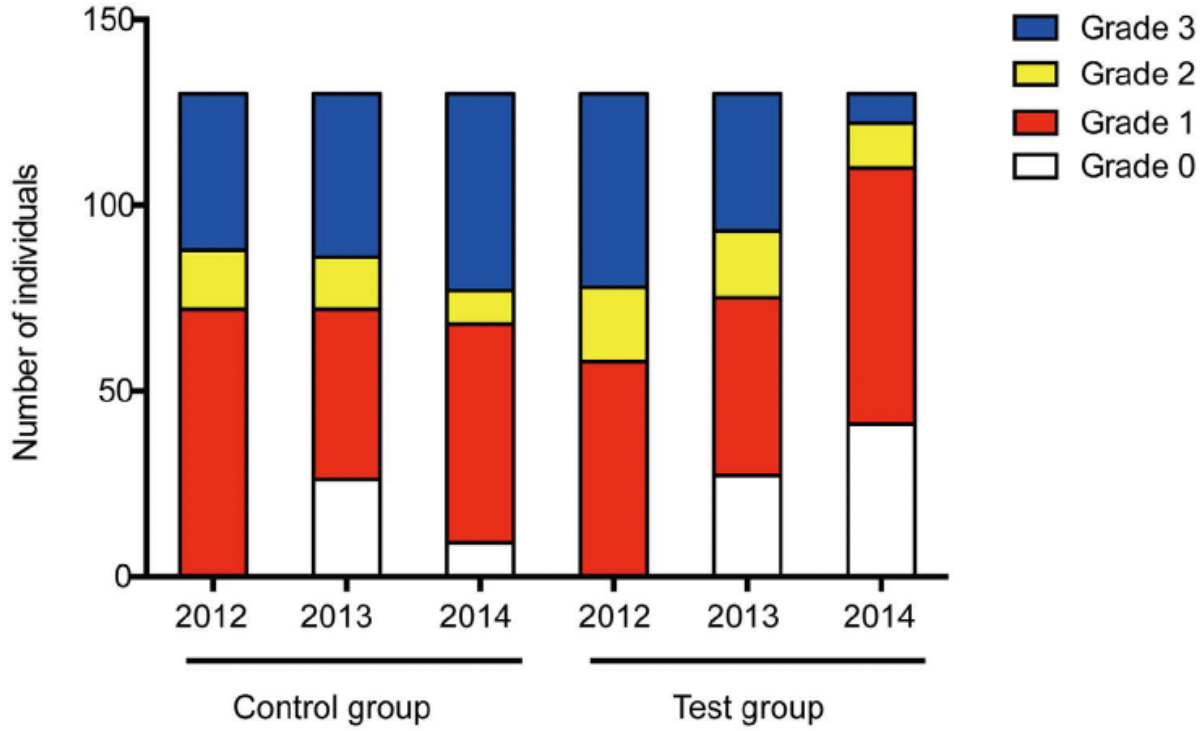


Figure 2. Changes in liver steatosis grade detected by liver ultrasound.

SCIENTIFIC REPORTS | 6:36783 | DOI: 10.1038/srep36783

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

247 adults with NASH and without diabetes
- ***Pioglitazone:*** 30 mg daily (80 subjects)
- ***Vitamin E***: 800 IU daily (84 subjects)
- ***Placebo*** (83 subjects)

Treatment: 96 weeks.

Improvement in NASH
Vitamin E vs placebo: 43% vs. 19%, P = 0.001

Pioglitazone vs placebo: 34% and 19% P = 0.04 (NS).

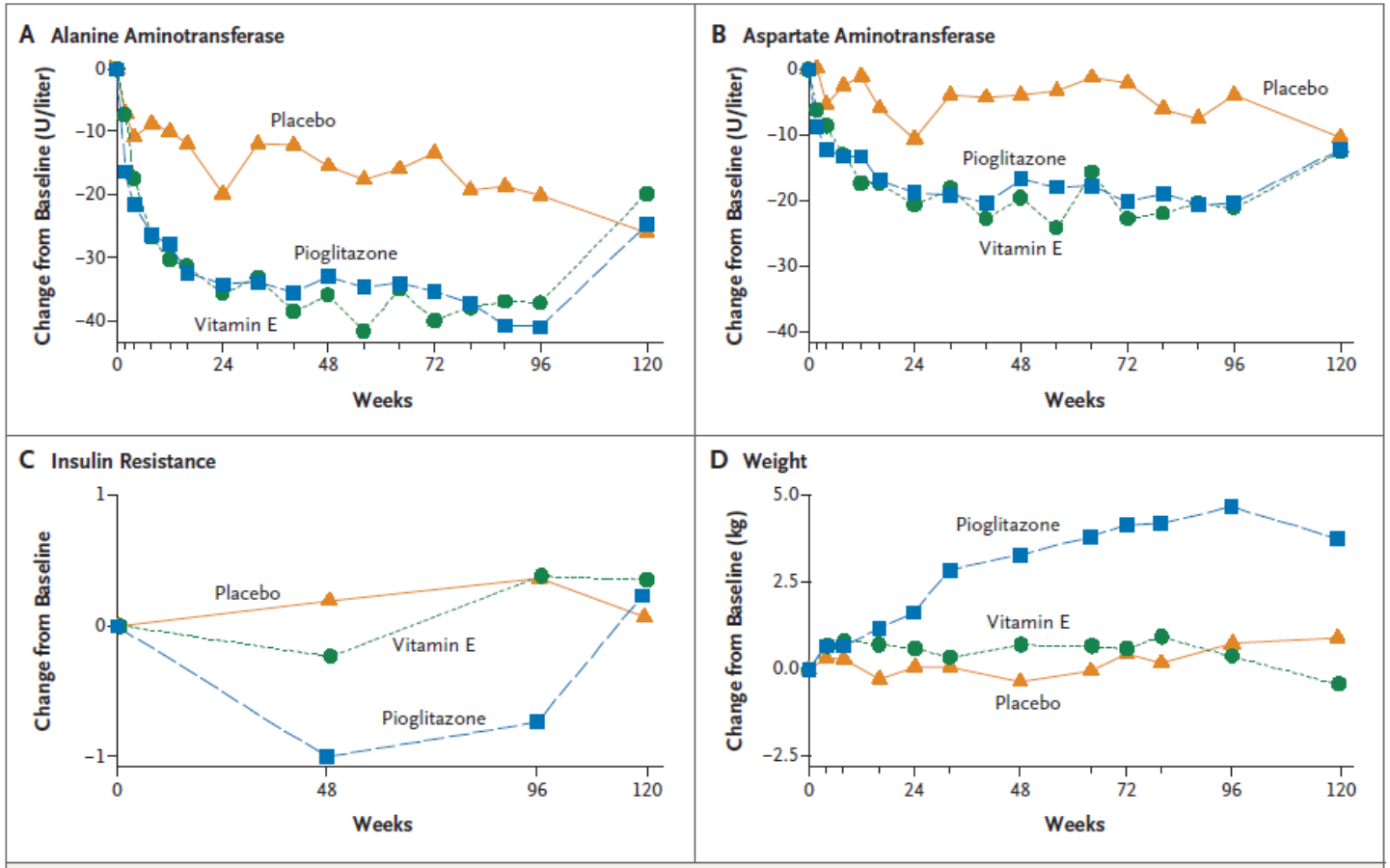


Figure 2. Changes from Baseline in Aminotransferase Levels, Insulin Resistance, and Weight, According to Study Group.

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La Clinica Terapeutica

Clin Ter. 2013 May-Jun;164(3):203-7. doi: 10.7417/CT.2013.1550.

The treatment with ursodeoxycholic acid in elderly patients affected by NAFLD and metabolic syndrome: a case-control study.

Troisi G[1], Crisciotti F, Gianturco V, D'Ottavio E, Lo Iacono C, Formosa V, Bernardini S, Bellomo A, Marigliano B, Marigliano V.

[1]Department of Cardiovascular, Respiratory, Nephrological and Geriatric Sciences, Rome University Sapienza, Rome, Italy.

Abstract

AIMS:

Evaluating the prevalence and the degree of steatosis in geriatric patients (65 to 85 years of age) with Metabolic Syndrome (defined by ATP III criteria); searching for metabolic factors which are predictive for the degree of steatosis; evaluating the efficacy of Ursodeoxycholic Acid (UDCA) for 6 months in the treatment of patients with NAFLD or NASH.

MATERIALS AND METHODS:

We studied 87 geriatric patients with Metabolic Syndrome. Steatosis was diagnosed and graded by laboratory assessment and ultrasonography, method based on the determination of liver/kidney ratio through grey-scale intensity, which was calculated as an index of the severity of the steatosis: it could oscilates from 0 (none) to 3 (severe). We randomized the geriatric patients into two groups: Ursodeoxycholic Acid (UDCA)-treated group (n=43 pz) and diet-treated group (1200 Kcal/die for female, 1500 Kcal/die for male) (n=44 pz), for a period of 6 months. BMI, principal symptoms, liver function, blood lipids, ultrasonography liver were evaluated respectively before and after treatment.

RESULTS:

The prevalence of steatosis was 100% (26 mild steatosis cases, 38 moderate cases and 23 severe cases) in our patients with Metabolic Syndrome. Of the 43 subjects assigned to receive 300-450 mg/d of UDCA and diet, the hepatic steatosis index decreased on the average, of the 75%. Serum AST, ALT and γ-GT decreased significantly at 3 months already ($p<0.001$).

CONCLUSIONS:

UDCA improves liver enzymes and ultrasonography imaging in geriatric patients with NAFLD or NASH. Unexpectedly, UDCA has resulted in beneficial effects on glycemic control and insulin sensitivity.

Table 3. How to manage NAFLD patients?

	AGA, AASLD, ACG [21]	CLDA [19]	IASL [20]	EASL [17]	APWP [18]
Weight loss	+ (3-5% to improve steatosis, 10% to improve NASH)	+ (more than 5%)	+ (0.5 Kg/wk)	+ (7%)	+
Hypocaloric diet	+	+ (500-1000 Kcal)	+	+	+
Alcohol	-,?	-	- (particularly in obese NAFLD)	?	/
Physical exercise	+	+ (4 times per week, 150 min of aerobic exercise)	+	+ (150 min/wk moderate and 75 min/wk vigorous exercise)	+
Educational therapy	/	+	+	+	/
Metformin	-	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)
Glitazones	+ (pioglitazone in non-diabetic biopsy-proven NASH)	- (not contraindicated in diabetic NAFLD)	- (not contraindicated in diabetic NAFLD)	+ (NASH)	- (not contraindicated in diabetic NAFLD)
Vitamin E	+ (in non-diabetic biopsy-proven NASH)	+	-	+ (NASH)	-
UDCA	-	+	-	+ (NASH)	-
Omega-3 FA	- (not contraindicated in hypertriglyceridemic NAFLD)	+	- (not contraindicated in hypertriglyceridemic NAFLD)	- (not contraindicated in hypertriglyceridemic NAFLD)	- (not contraindicated in hypertriglyceridemic NAFLD)
Statins	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)	- (not contraindicated in dyslipidemic NAFLD)
Bariatric surgery	- (not contraindicated in eligible obese NAFLD)	+ (in obese patients refractory to medical measures)	- (reserved to controlled studies)	+ (in morbidly obese advanced fibrotic NASH)	+ (in obese patients refractory to medical measures)

+, recommended; –, not recommended; /, not mentioned.

Nascimbeni F et al., J Hepatol 2013; 59: 859-871

No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial

Ilaria Barchetta[1], Maria Del Ben[1], Francesco Angelico[1], Michele Di Martino[2], Antonio Fraioli[1], Giuseppe La Torre[3], Rosella Saulle[3], Ludovica Perri[1], Sergio Morini[4], Claudio Tiberti[5], Laura Bertoccini[5], Flavia Agata Cimini[1], Francesca Panimolle[5], Carlo Catalano[2], Marco Giorgio Baroni[5,6] and Maria Gisella Cavallo[1*]

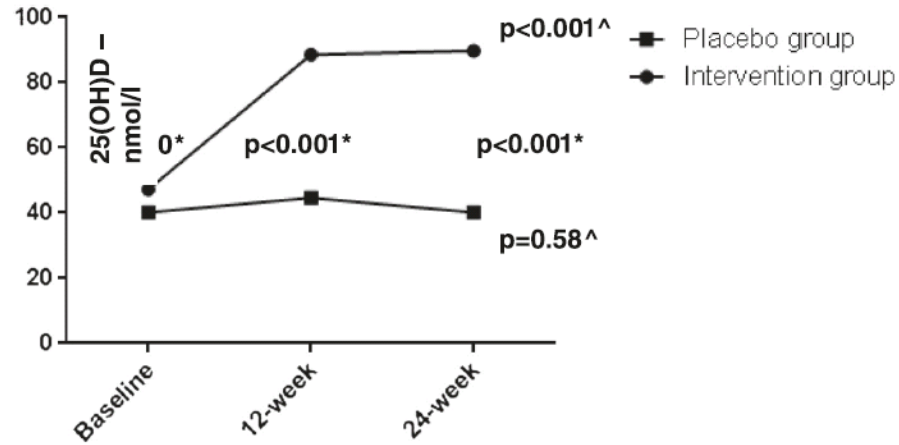

Fig. 3 Serum 25(OH) D levels in intervention versus placebo group. * Independent samples U Mann–Whitney's test; ^ Multiple dependent comparisons Friedman's test

Results: Sixty-five patients were randomized, 26 (cholecalciferol) and 29 (placebo) subjects completed the study. 25(OH) vitamin D significantly increased in the active treated group (48.15 ± 23.7 to 89.80 ± 23.6 nmol/L, $P < 0.001$); however, no group differences were found in HFF, transaminases, CK18-M30, P3NP levels or FLI after 24 weeks. Vitamin D neither changed the metabolic profile nor the cardiovascular parameters.

Conclusions: Oral high-dose vitamin D supplementation over 24 weeks did not improve hepatic steatosis or metabolic/cardiovascular parameters in T2D patients with NAFLD. Studies with a longer intervention period are warranted for exploring the effect of long time exposure to vitamin D.

Barchetta *et al. BMC Medicine* (2016) 14:92
DOI 10.1186/s12916-016-0638-y

Steatosi Epatica e Dismetabolismi nell'Anziano
Messaggi conclusivi

Le alterazioni del metabolismo associate all'invecchiamento sono complesse e tuttora non completamente conosciute

La NAFLD nell'anziano è verosimilmente legata ad alterazioni metaboliche (insulino-resistenza, alterazioni ormoni sessuali) ed infiammatorie associate all'invecchiamento

Gli stessi fattori (con)causali potrebbero essere in relazione con altre sindromi di interesse geriatrico

La terapia della NAFLD nell'anziano si basa principalmente sull'approccio igienico-dietetico (per quanto praticabile); la terapia farmacologica di condizioni associate (dislipidemia, diabete, ipertensione) non è, di norma, controindicata

University of Modena and Reggio Emilia

Department of Biomedical, Metabolic
and Neural Sciences

THANK YOU !

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Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

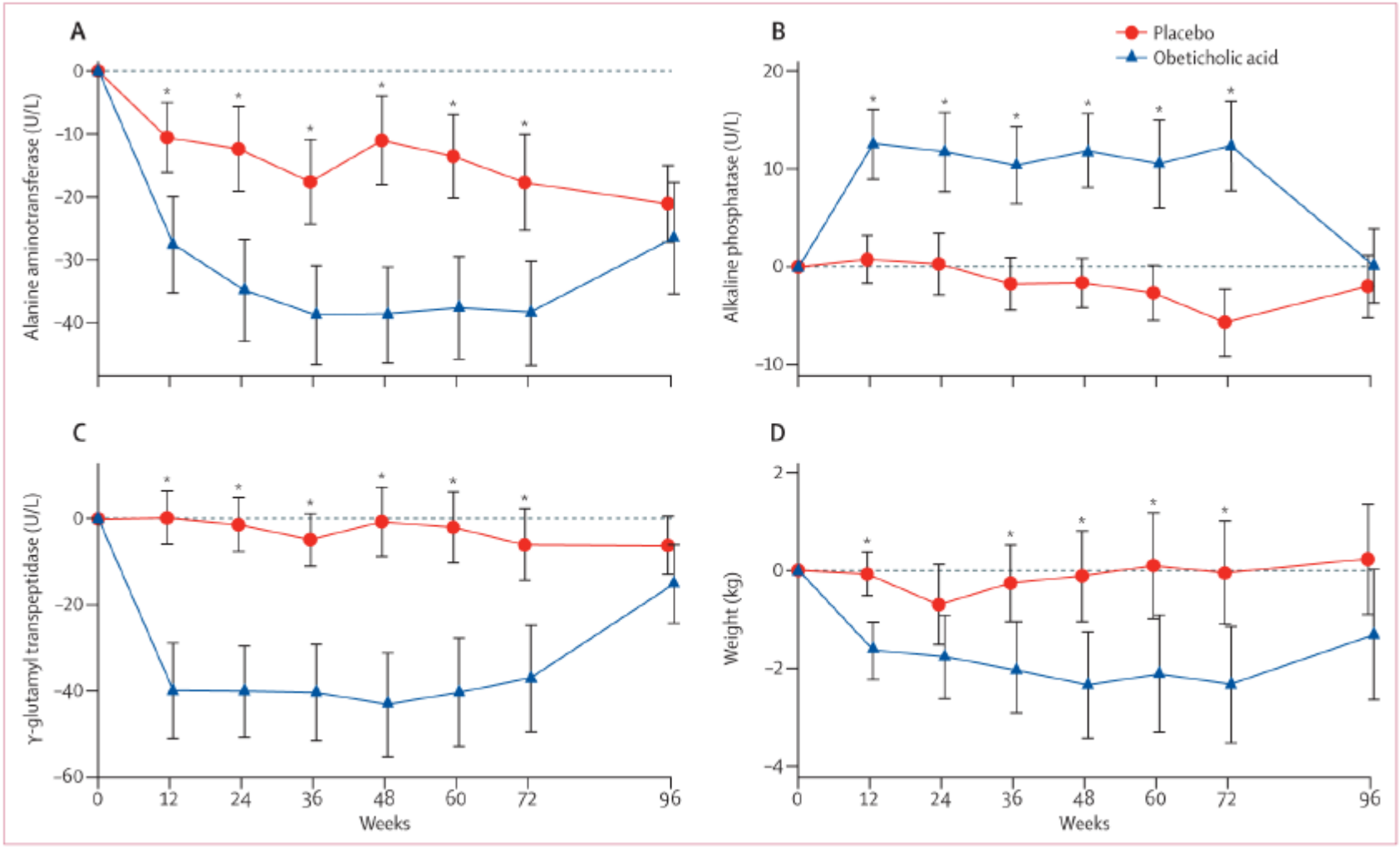

Figure 2. Changes from baseline in liver enzymes and bodyweight according to treatment group

Changes in histological features of the liver after 72 weeks of treatment

	Obeticholic acid	Placebo	Relative risks or mean changes from baseline* (95% CI) (obeticholic acid *vs* placebo)	p value*
Primary outcome†				
Number of patients at risk‡	110	109		
Patients with improvement	50 (45%)	23 (21%)	1·9 (1·3 to 2·8)	0·0002
Changes from baseline in histological features				
Number of patients with biopsy specimens at baseline and 72 weeks	102	98		
Resolution§ of definite non-alcoholic steatohepatitis	22 (22%)	13 (13%)	1·5 (0·9 to 2·6)	0·08
Fibrosis¶				
Patients with improvement	36 (35%)	19 (19%)	1·8 (1·1 to 2·7)	0·004
Change in score	−0·2 (1·0)	0·1 (0·9)	−0·3 (−0·6 to −0·1)	0·01
Total NAFLD activity score				
Change in score	−1·7 (1·8)	−0·7 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Hepatocellular ballooning				
Patients with improvement	47 (46%)	30 (31%)	1·5 (1·0 to 2·1)	0·03
Change in score	−0·5 (0·9)	−0·2 (0·9)	−0·2 (−0·5 to 0·0)	0·03
Steatosis				
Patients with improvement	62 (61%)	37 (38%)	1·7 (1·2 to 2·3)	0·001
Change in score	−0·8 (1·0)	−0·4 (0·8)	−0·4 (−0·6 to −0·2)	0·0004
Lobular inflammation				
Patients with improvement	54 (53%)	34 (35%)	1·6 (1·1 to 2·2)	0·006
Change in score	−0·5 (0·8)	−0·2 (0·9)	−0·3 (−0·5 to −0·1)	0·0006
Portal inflammation‖				
Patients with improvement	12 (12%)	13 (13%)	1·0 (0·6 to 1·7)	0·90
Change in score	0·2 (0·7)	0·2 (0·7)	0·0 (−0·1 to 0·2)	0·59

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Lancet. 2015 March 14; 385(9972): 956–965. doi:10.1016/S0140-6736(14)61933-4.

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Effetti di Acido Obeticolico in NASH:

- Miglioramento del profilo enzimi (ma aumento AlkP)
- Miglioramento dell'istologia
- Peggioramento del profilo lipidico (aumento TotC, LDL-C, riduzione HDL-C)

Long-term studies are needed

Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The Lira-NAFLD study

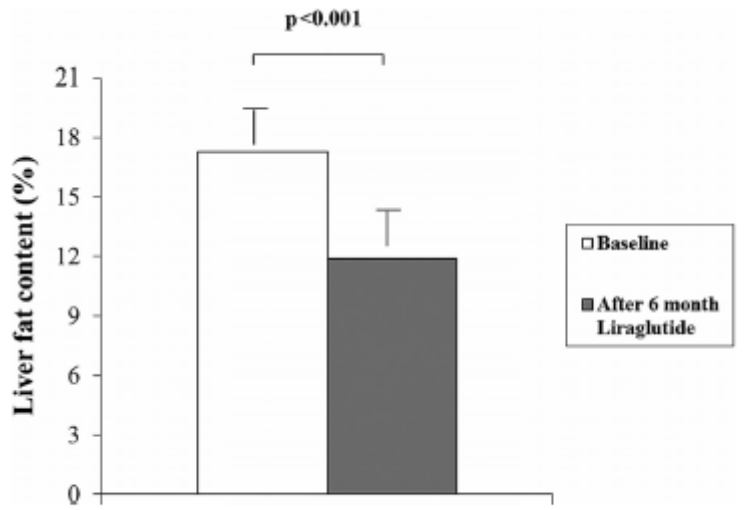


Figure 1. Liver fat content in patients with type 2 diabetes before and 6 months after the initiation of liraglutide treatment

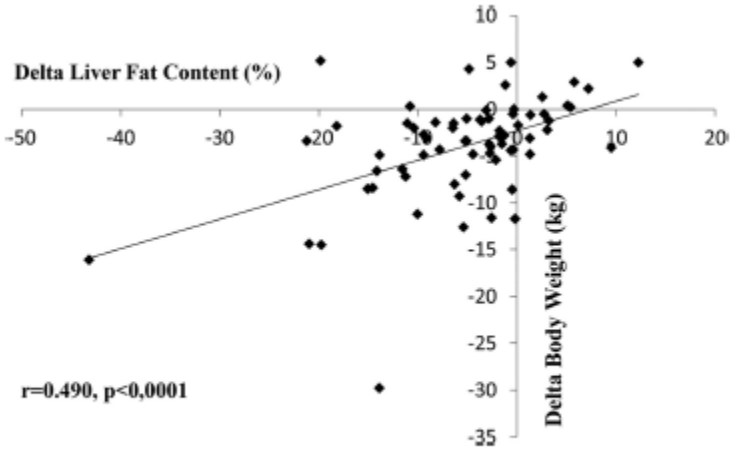


Figure 2. Correlation between reduction in liver fat content and reduction in body weight

doi: 10.1210/jc.2016-2775 J Clin Endocrinol Metab press.endocrine.org/journal/jcem

ECHOCARDIOGRAPHY AND DUAL-ENERGY X-RAY ABSORPTIOMETRY IN THE ELDERLY PATIENTS WITH METABOLIC SYNDROME: A COMPARISON OF TWO DIFFERENT TECNIQUES TO EVALUATE VISCERAL FAT DISTRIBUTION

G. STRAMAGLIA[1], A. GRECO[2], G. GUGLIELMI[3], A. DE MATTHAEIS[2], G.L. VENDEMIALE[1-2]

Table 3

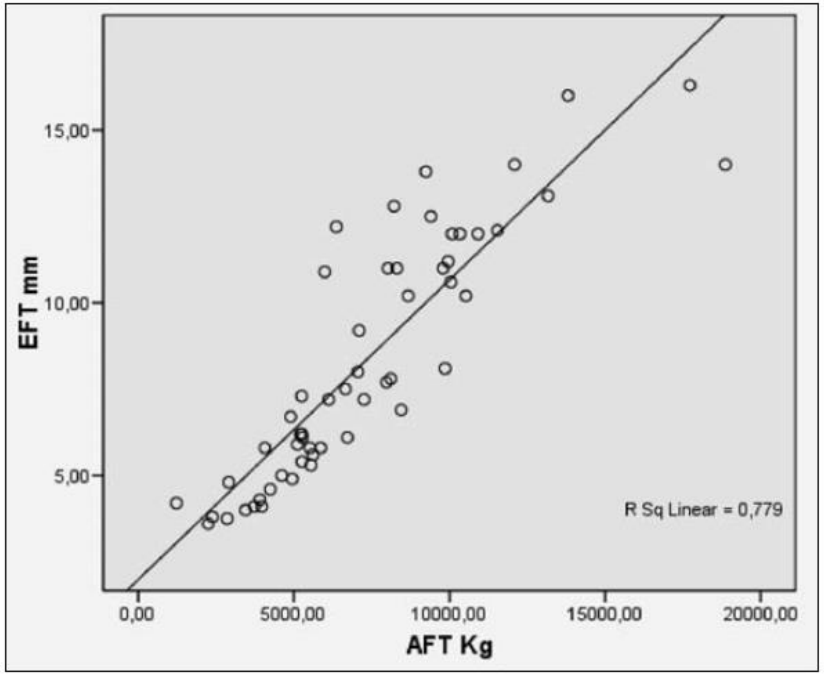
Body composition in MetS vs non MetS patients

VARIABLE	Non MetS patients n= 24	MetS patients n= 31	p
AFT (Kg)	5.4±0.4	9.7±0.7	p<0.01
FFT (Kg)	16.9±0.6	14.1±0.6	p<0.05
EFT (mm)	6.2±0.4	11.0±0.5	p<0.01

AFT= abdominal fat tissue (kg); FFT= fat free mass (kg); EFT: epicardial fat (mm)

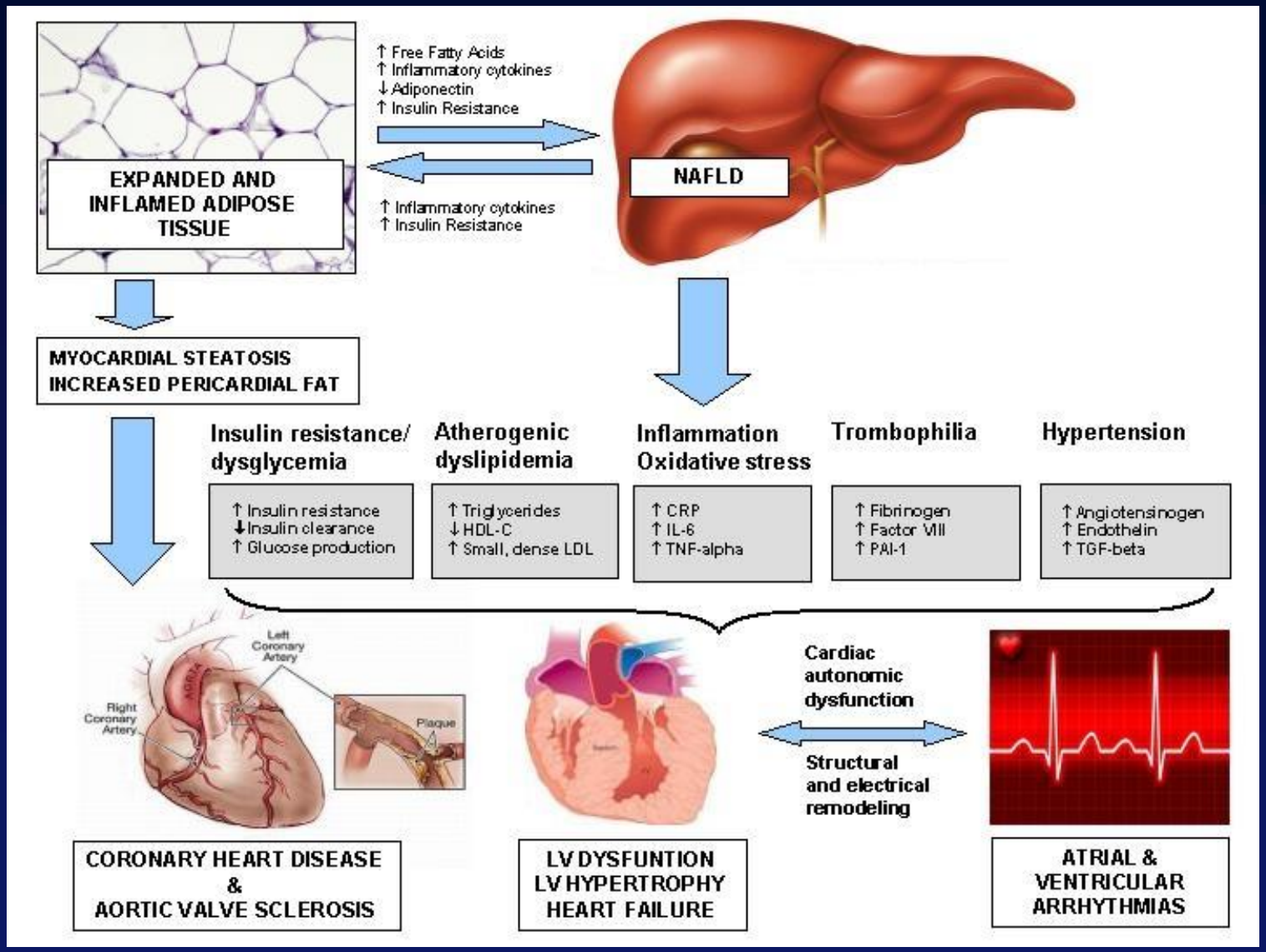
Figure 2

Correlation between epicardial fat (EFT) measured by echocardiography and abdominal fat mass (AFT) measured by X Ray Dual Absorbiometry (DEXA)



The Journal of Nutrition, Health & Aging©
Volume 14, Number 1, 2010

The expanding spectrum of CV manifestations of NAFLD



Ballestri, Lonardo & Targher WJG 2014; 20:1724-45.