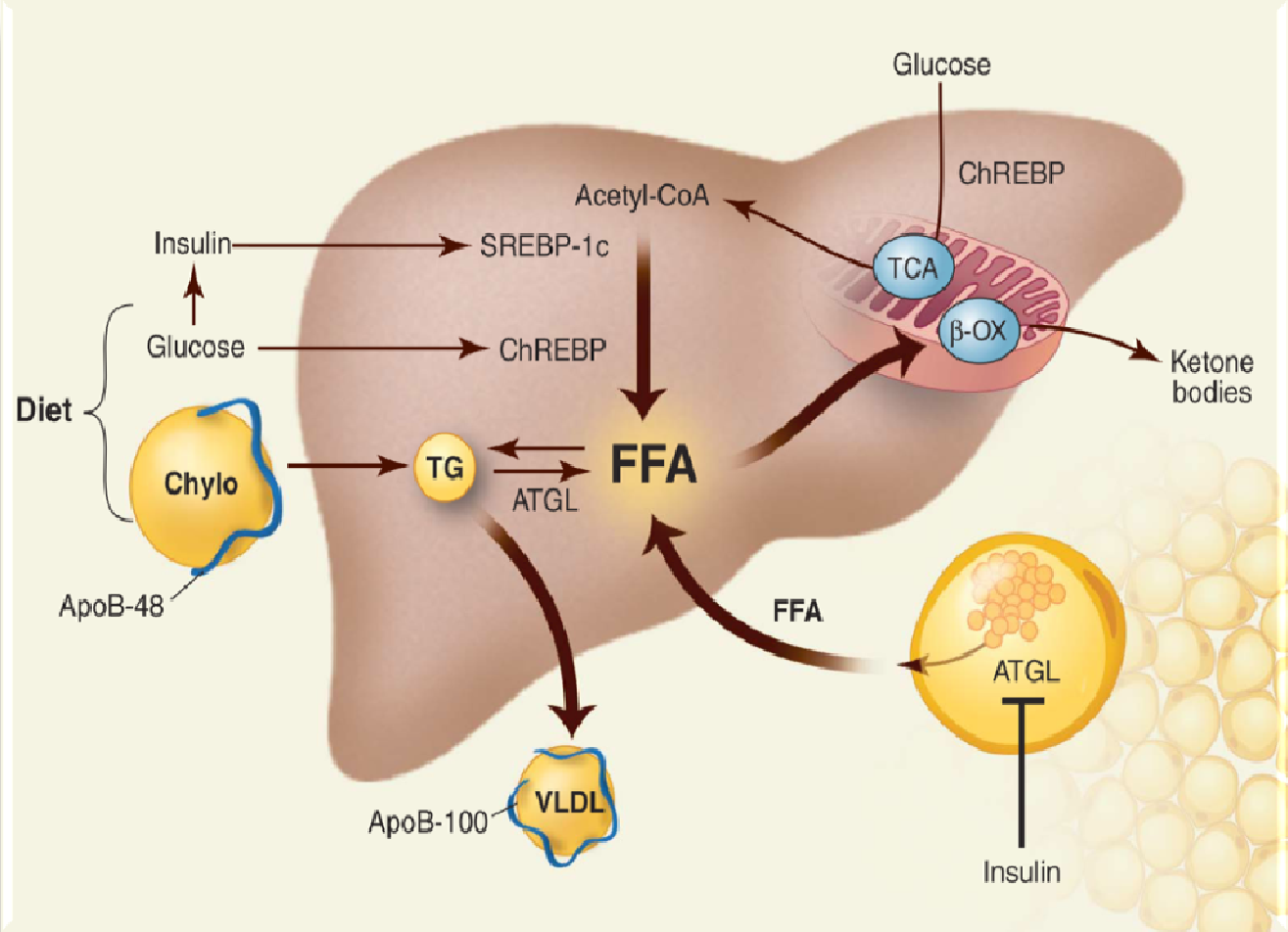
Steatosi e stress ossidativo: approccio terapeutico con nutraceutici

NAFLD e insulino-resistenza



- Aumentata sintesi TGL (steatosi)
- Aumentata ossidazione (stress ossidativo)

Cohen JC et al. Science 2011

Hindawi Publishing Corporation
International Journal of Cell Biology
Volume 2014, Article ID 519153, 9 pages
http://dx.doi.org/10.1155/2014/519153

Review Article

An Intimate Relationship between ROS and Insulin Signalling: Implications for Antioxidant Treatment of Fatty Liver Disease

Aurèle Besse-Patin[1,2] and Jennifer L. Estall[1,2]

[1] *Division of Cardiovascular and Metabolic Diseases, Institut de Recherches Cliniques de Montreal 110, Avenue des Pins Ouest, Montreal, QC, Canada H2W 1R7*
[2] *Molecular Biology Department, University of Montreal, Montreal, QC, Canada H3C 3J7*

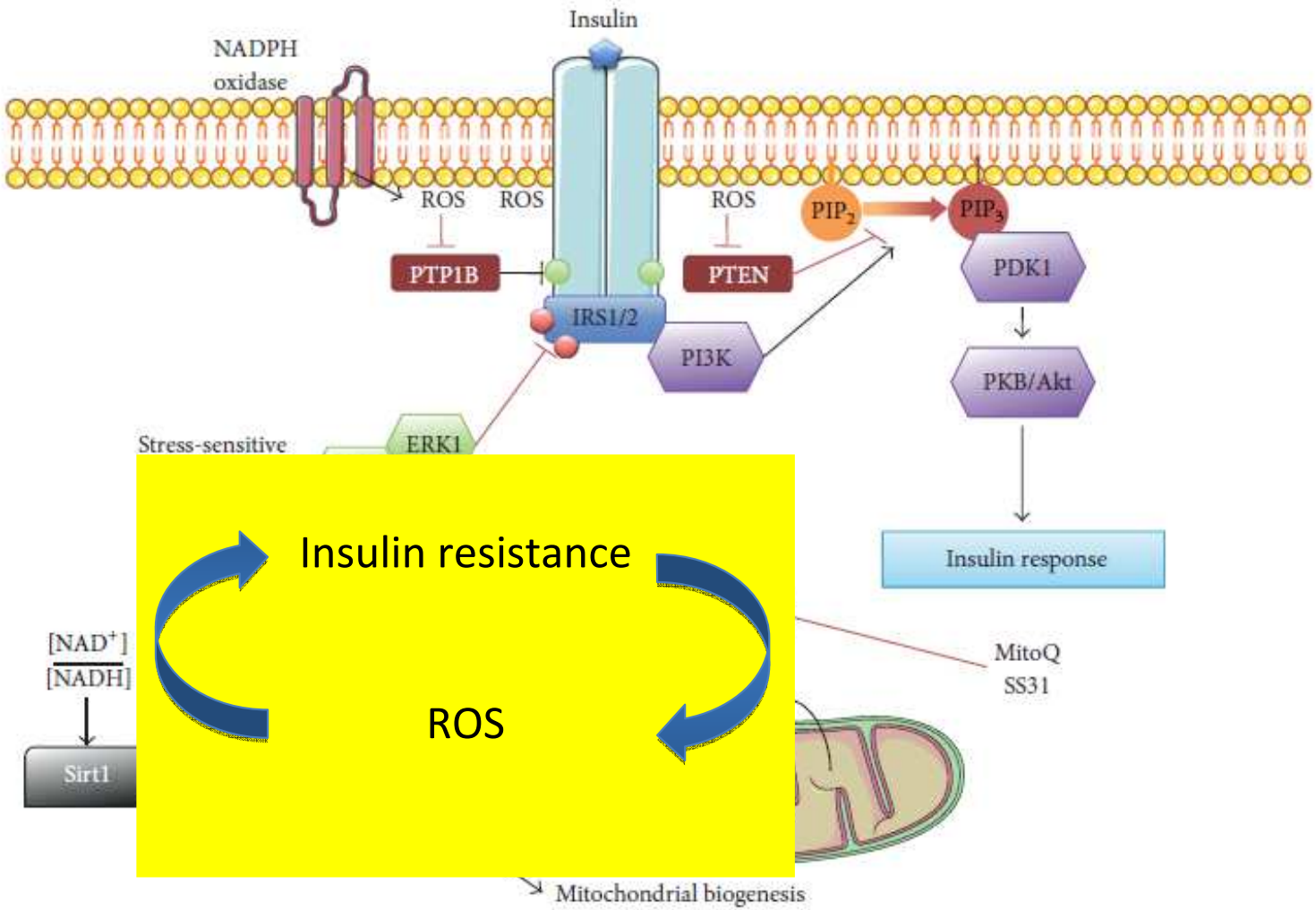


FIGURE 1: Molecular mechanisms linking ROS, antioxidants, and the insulin signalling pathway. To allow a response to insulin stimulation, ROS are relieving insulin receptor's inhibition by phosphatases such as PTP1B. When the cellular environment shifts to an oxidative one, because of increased mitochondrial respiration and ROS release for example, the stress-sensitive kinases are activated upon redox-sensitive phosphatases inhibition. Theses kinases are inhibiting signal amplification by inhibitory phosphorylation of IRS proteins. Mitochondrial ROS can be regulated by PGC-1α-dependent detoxification system (Sirt3, SOD, GPx) or by specific mitochondrial antioxidants (SS31, MitoQ).

Opzioni terapeutiche per NAFLD

Approccio metabolico (reversibilità della steatosi)

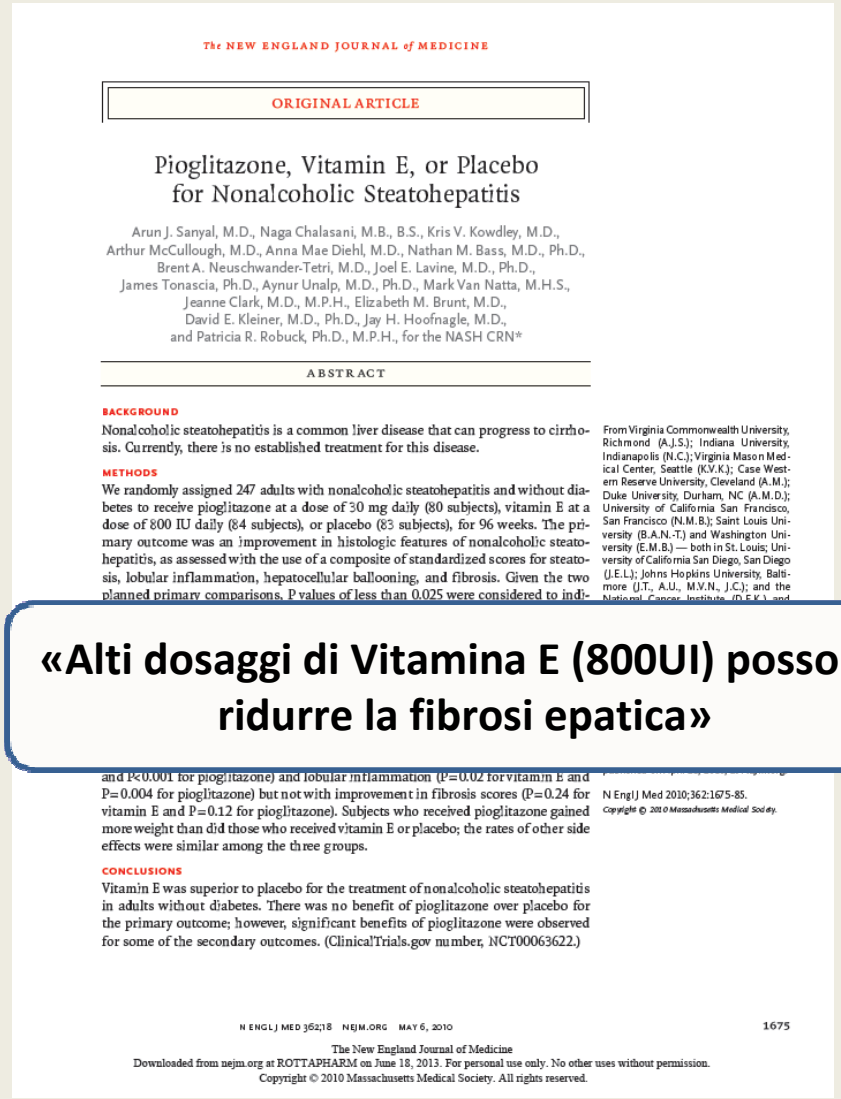
Dieta, esercizio fisico

Insulino-sensibilizzanti **(metformina, pioglitazone)**
-possono ridurre la steatosi in pazienti con insulino-resistenza

Ipolipemizzanti (**Statine, ezetimibe**)
Possono ridurre la steatosi

Vitamina E

Stress ossidativo → **Fibrosi**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

ABSTRACT

BACKGROUND

Nonalcoholic steatohepatitis is a common liver disease that can progress to cirrhosis. Currently, there is no established treatment for this disease.

METHODS

We randomly assigned 247 adults with nonalcoholic steatohepatitis and without diabetes to 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. The 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. Given the two planned primary comparisons, P values of less than 0.025 were considered to indi-

and P<0.001 for pioglitazone) and lobular inflammation (P=0.02 for vitamin E and P=0.004 for pioglitazone) but not with improvement in fibrosis scores (P=0.24 for vitamin E and P=0.12 for pioglitazone). Subjects who received pioglitazone gained more weight than did those who received vitamin E or placebo; the rates of other side effects were similar among the three groups.

CONCLUSIONS

Vitamin E was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes. There was no benefit of pioglitazone over placebo for the primary outcome; however, significant benefits of pioglitazone were observed for some of the secondary outcomes. (ClinicalTrials.gov number, NCT00063622.)

From Virginia Commonwealth University, Richmond (A.J.S.); Indiana University, Indianapolis (N.C.); Virginia Mason Medical Center, Seattle (K.V.K.); Case Western Reserve University, Cleveland (A.M.); Duke University, Durham, NC (A.M.D.); University of California San Francisco, San Francisco (N.M.B.); Saint Louis University (B.A.N.-T.) and Washington University (E.M.B.) — both in St. Louis; University of California San Diego, San Diego (J.E.L.); Johns Hopkins University, Baltimore (J.T., A.U., M.V.N., J.C.); and the

N Engl J Med 2010;362:1675-85.

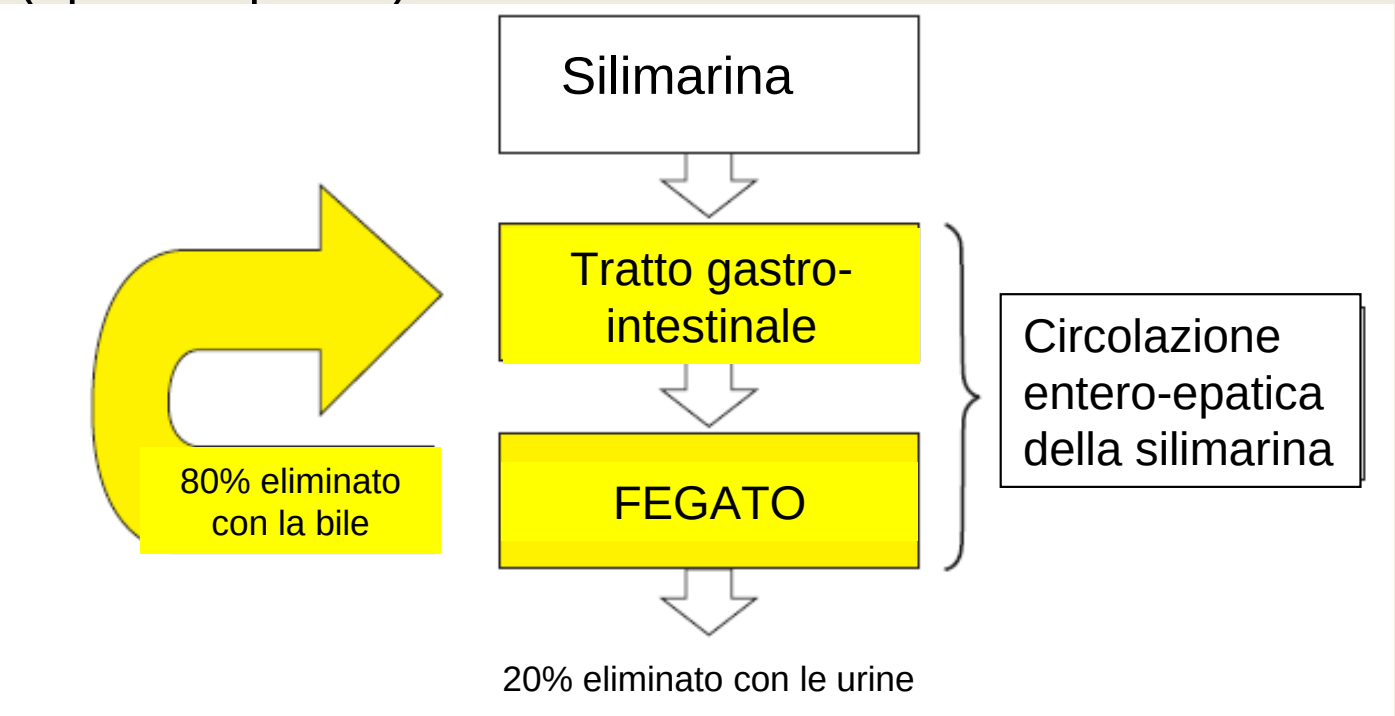
«Alti dosaggi di Vitamina E (800UI) possono ridurre la fibrosi epatica»

Sanyal et al, NEJM 2010

Farmacocinetica: epatotropismo della silimarina

Picco ematico raggiunto 1.5 h dopo somministrazione orale, con emivita di 6.0 ore.

Poichè entra nella circolazione entero-epatica, la silimarina si accumula nel fegato (epato-tropismo).

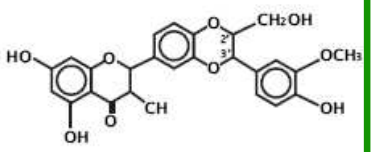


Hawke RL et al. Silymarin Ascending Multiple Oral Dosing Phase I Study J. Clinical Pharmacol 2010; 50; 434-449

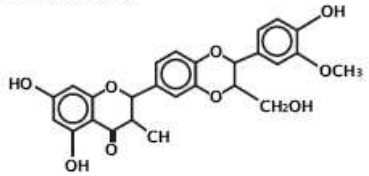
semi

Estrazione

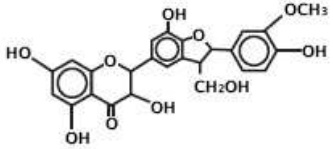
Silibinin



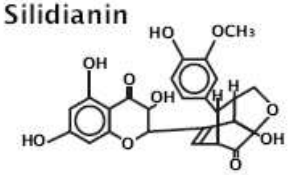
Isosilibinin



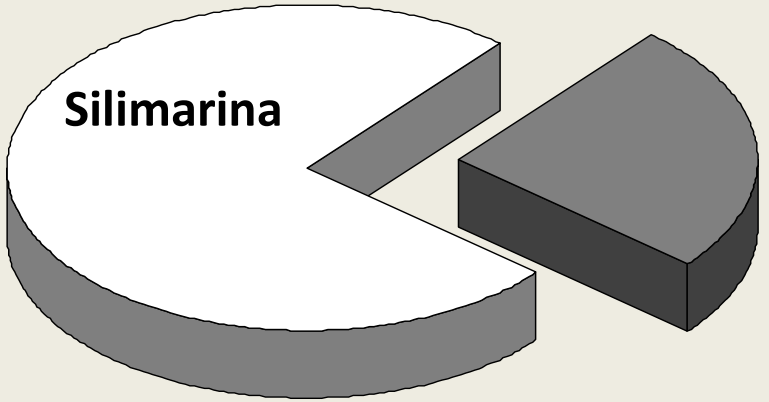
Silicristin



Silidianin

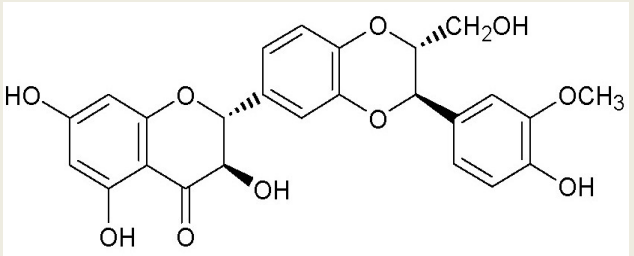


Silimarina



Componente + attivo

Silibinina



Nuovi sviluppi con silibinina I.V. (Legalon-SIL)

EMEA

US FDA

Hanno attribuito a Legalon-SIL lo stato di «**Orphan drug»**

Per la prevenzione della **re-infezione con HCV in pazienti con trapianto di fegato**

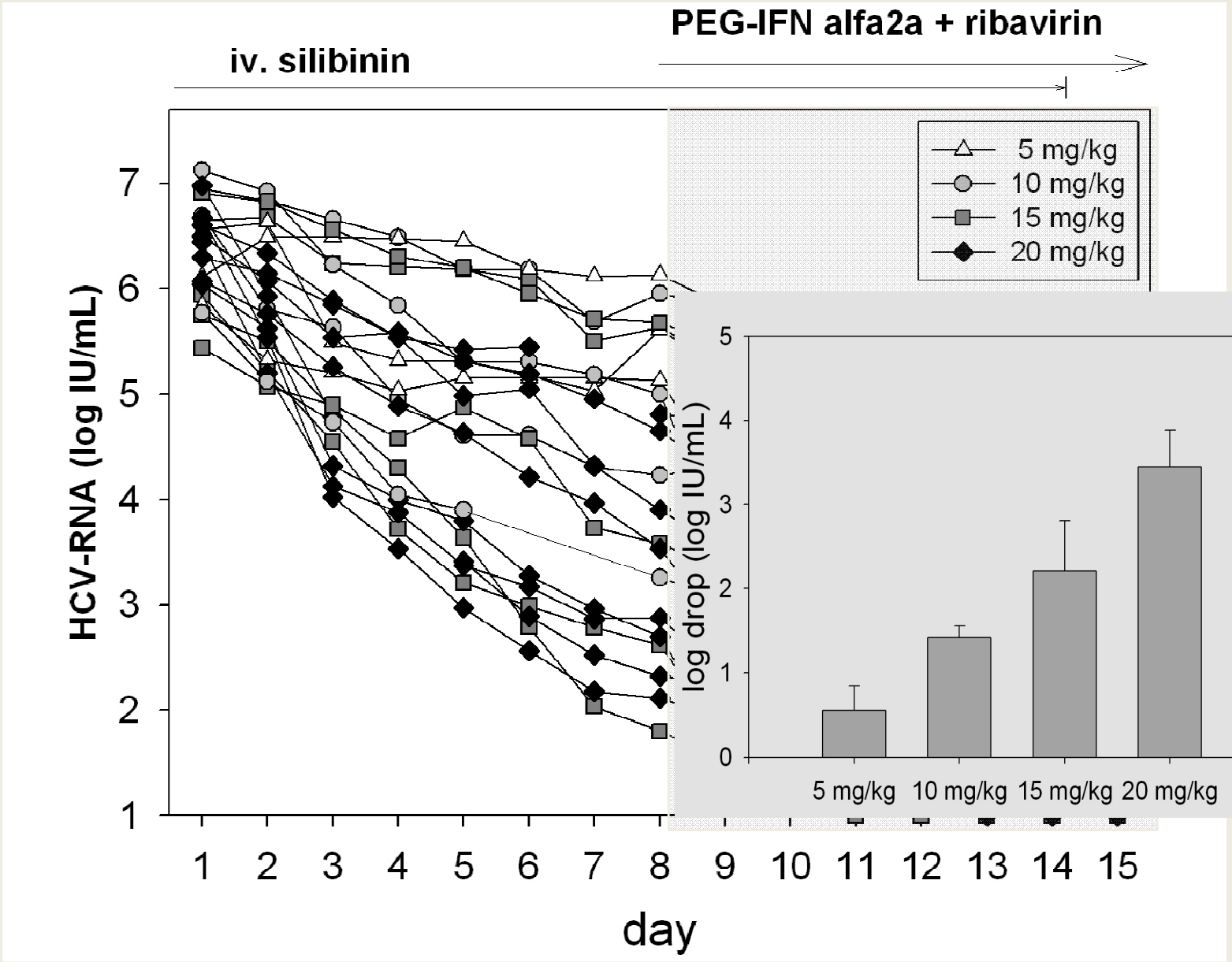
Legalon-SIL (dosaggio molto alto, i.v.)
Ha una potente attività antivirale in pazienti con epatite C cronica

Silibinin Is a Potent Antiviral Agent in Patients With Chronic Hepatitis C Not Responding to Pegylated Interferon/Ribavirin Therapy

Peter Ferenci,[1] Thomas-Matthias Scherzer,[1] Heidrun Kerschener,[2] Karoline Rutter,[1] Sandra Beinhardt,[1] Harald Hofer,[1] Maximilian Schöniger-Hekele,[1] Heidemarie Holzmann,[2] and Petra Steindl-Munda[1]

[1]Internal Medicine 3, Department of Gastroenterology and Hepatology, Medical University of Vienna, Austria; and [2]Clinical Institute of Virology, Medical University of Vienna, Austria.

Gastroenterology 2008; 135:1561-1567


PEG-IFN alfa2a + ribavirin
iv. silibinin
5 mg/kg
10 mg/kg
15 mg/kg
20 mg/kg
HCV-RNA (log IU/mL)
day
log drop (log IU/mL)
5 mg/kg
10 mg/kg
15 mg/kg
20 mg/kg

Conferma «virologica» del meccanismo d'azione: inibizione RNA polimerasi

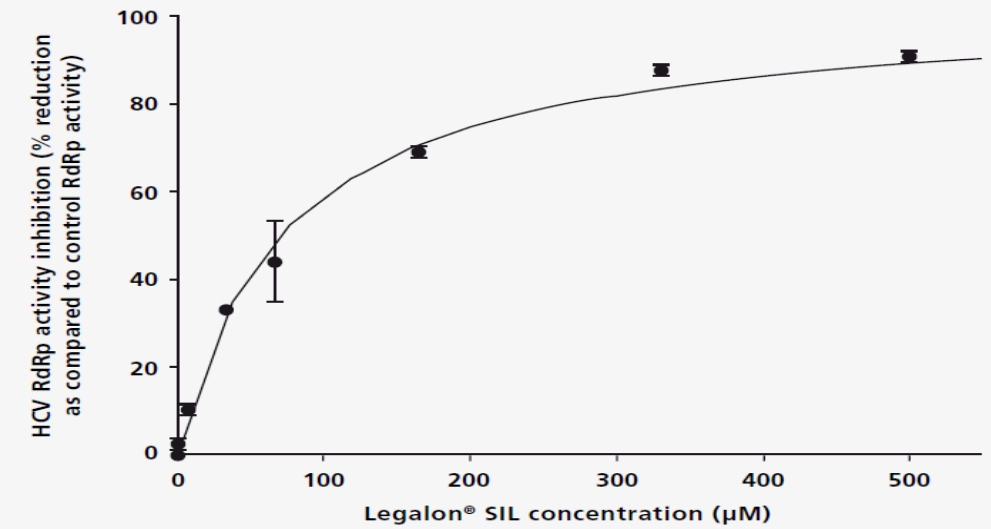
Silibinin and Related Compounds Are Direct Inhibitors of Hepatitis C Virus RNA-Dependent RNA Polymerase

Abdelhakim Ahmed-Belkacem,[1] Nazim Ahnou,[1] Laetitia Barbotte,[1] Czeslaw Wychowski,[2] Coralie Pallier,[1,3] Rozenn Brillet,[1] Ralf-Torsten Pohl,[4] and Jean-Michel Pawlotsky[1,5]

[1]Research Team "Pathophysiology and Therapy of Chronic Viral Hepatitis", INSERM U955, Créteil, France;
[2]Institut de Biologie de Lille (CNRS UMR8161), Université de Lille I & II and Institut Pasteur de Lille, Lille, France ;
[3]Department of Virology, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France; [4]Rottapharm|Madaus, Cologne, Germany ;
[5]National Reference Center for Viral Hepatitis B, C and Delta, Department of Virology, Hôpital Henri Mondor, Université Paris 12, Créteil, France.

Gastroenterology 2010; 138:1112-1122

Silibinin inhibition of the HCV RNA-dependent RNA polymerase (RdRp)



Rapid Suppression of Hepatitis C Viremia Induced by Intravenous Silibinin Plus Ribavirin

Michael Biermer, Thomas Berg

Medizinische Klinik m. S. Hepatologie und Gastroenterologie. Charité Campus Virchow Universitätsmedizin Berlin, Germany

Gastroenterology 2009; 137:390-391

Successful HCV eradication and inhibition of HIV replication by intravenous silibinin in an HIV–HCV coinfected patient

B.A. Payer, T. Reiberger, K. Rutter, S. Beinhardt, A.F. Staettermayer, M. Peck-Radosavljevic, P. Ferenci

Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology & Hepatology, Waehringer Guertel 18-20, A1090 Vienna, Austria

Journal of Clinical Virology 2010; 49: 131-133

Intravenous silibinin as "rescue treatment" for on-treatment non-responders to pegylated interferon/ribavirin combination therapy

Karoline Rutter,[1] Thomas-Matthias Scherzer,[1] Sandra Beinhardt,[1] Heidrun Kerschner,[2] Albert F Stättermayer,[1] Harald Hofer,[1] Theresia Popow-Kraupp,[2] Petra Steindl-Munda,[1] Peter Ferenci[1*]

[1]Department of internal Medicine, Gastroenterology and Hepatology, Medical University of Vienna, Austria
[2]Department of Laboratory Medicine, Division of Clinical Virology, Medical University of Vienna, Austria

Antiviral Therapy 2011, 16: 1327-1333

Treatment of Hepatitis C-Virus-Reinfection After Liver Transplant with Silibinin in Nonresponders to Pegylated Interferon-based Therapy

Dennis Euri … **el Biermer[3],**

[1]Dept … many;
[2]Dept. of Intern … zig, Germany;
[3]Dept. of Interna… Berlin, Germany.

… and Clinical Transplantation 2011; 1: 1-6

Silibinin mon… … er orthotopic liver trans… … epatitis C

Sandra Beinhardt[1], … **rzer[1], Peter Ferenci[1]**

[1]Internal Medicin… … f Vienna, Austria.
[2]Divisio… … Austria.

… nal off Hepatology 2011; 54: 591-592

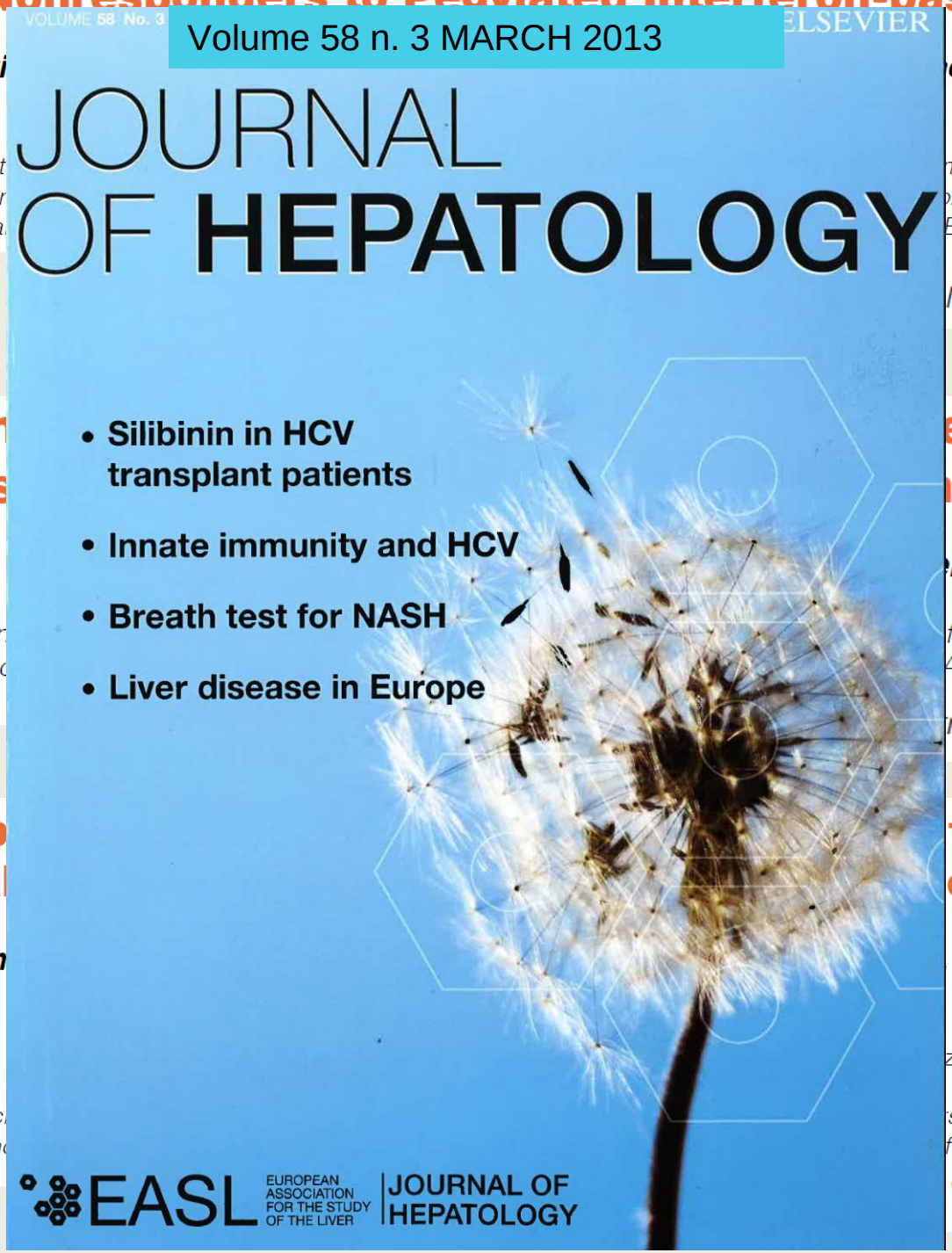
High-dose silib… … tients showing suboptimal… … on therapy

M. Biern… … **Heyne,[2]**

[1]Sektion Hepatologie, … zig, Leipzig, Germany,

[3]Medizinische Klinik mit Sc… … sitätsmedizin Berlin, Berlin, Germany; an… … furt, Germany

… Viral Hepatitis 2012; 19: 547-553



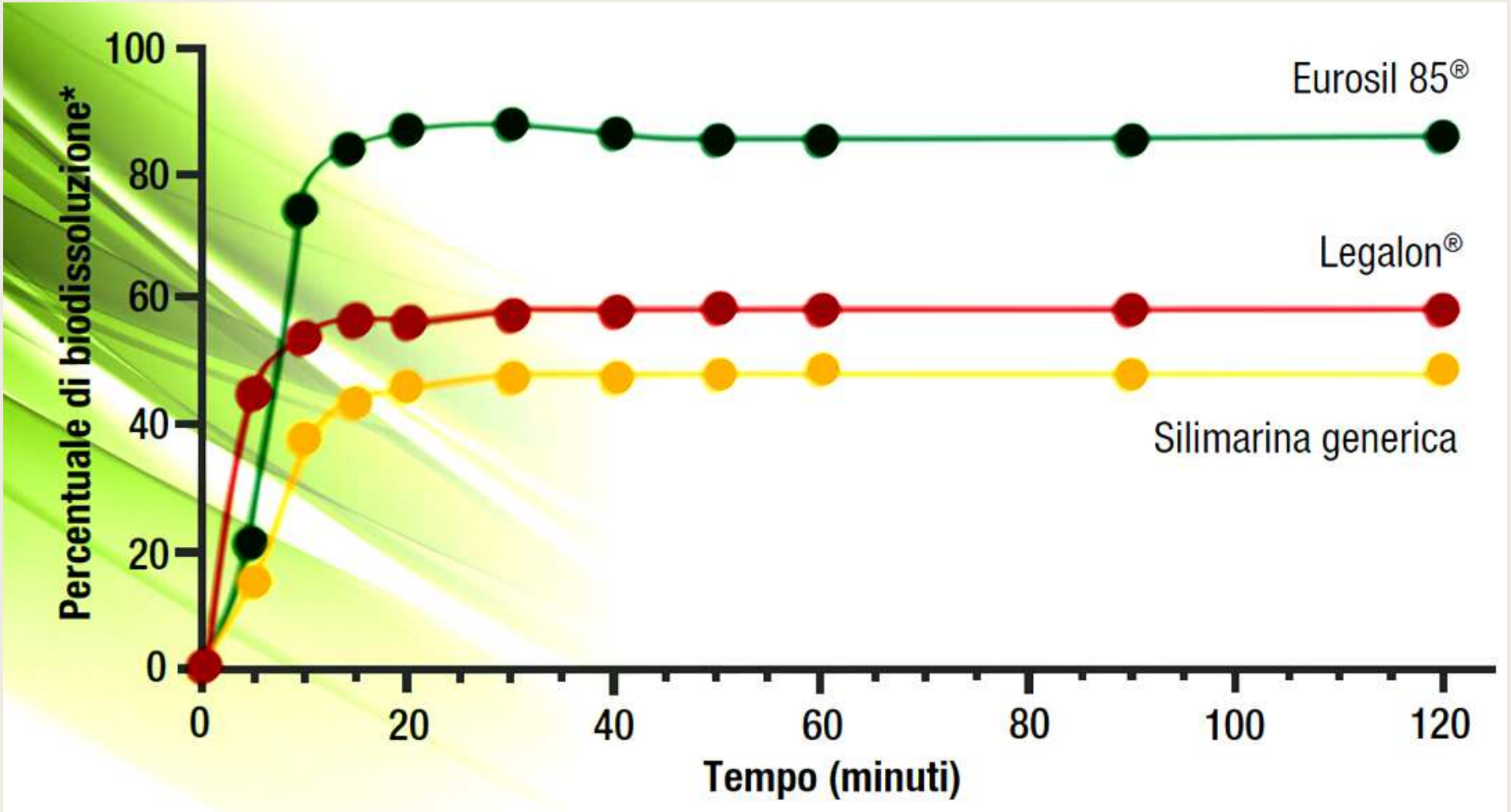
semi

Estrazione

Via orale:

Formulazione in cui la silibinina viene veicolata in modo naturale da altri isomeri «carrier»

Eurosil 85


Percentuale di biodissoluzione*
100
80
60
40
20
0
0
20
40
60
80
100
120
Tempo (minuti)
Eurosil 85®
Legalon®
Silimarina generica

A -- Silymarin Product Development Program for use in NIH-Sponsored Clinical Trial for Liver Diseases

Solicitation Number: Reference-Number-DK-05-0130

Agency: Department of Health and Human Services
Office: National Institutes of Health
Location: Nat'l Institute of Diabetes, Digestive, & Kidney Diseases

Notice Type:
Special Notice

Original Posted Da
March 3, 2005

Posted Date:
March 22, 2005

Response Date:
June 6, 2005

DESCRIPTION: The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and of the Department of Health and Human Services (DHHS) seek collaboration with industry to participate in the Silymarin Product Development Program for use of silymarin, derived from the milk thistle plant Silybum marianum, in NIH-sponsored clinical trials for liver diseases.

PUBLIC HEALTH SERVICE
EXTRAMURAL
CLINICAL TRIAL AGREEMENT

This Clinical Trial Agreement, hereinafter referred to as the "CTA," consists of this Agreement, a Signature Page, and various Appendices referenced in the Agreement. The Parties to this CTA are:

(1) The **National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health,** hereinafter referred to as "**NCCAM**", and

(2) Madaus GmbH (Madaus), having offices at Colonia Allee 15, 51067 Cologne, Germany hereinafter referred to as "**Collaborator**"

Eurosil 85:

Epatotropismo (HSC come target cellulare?)

ELSEVIER

Journal of Hepatology 50 (2009) 1102–1111

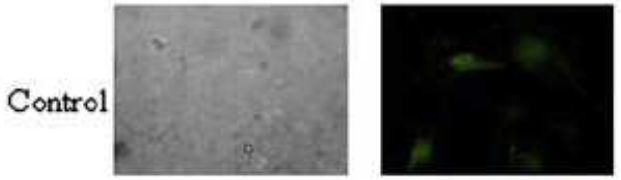
Journal of Hepatology

www.elsevier.com/locate/jhep

Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells☆

Marco Trappoliere[1], Alessandra Caligiuri[1], Monika Schmid[1], Cristiana Bertolani[1], Paola Failli[2], Francesco Vizzutti[1], Erica Novo[3], Carlo di Manzano[4], Fabio Marra[1,6], Carmela Loguercio[5], Massimo Pinzani[1,6,*]

[1] *Dipartimento di Medicina Interna, Università degli Studi di Firenze, Viale G.B. Morgagni, 85, 50134 Florence, Italy*
[2] *Dipartimento di Farmacologia Preclinica e Clinica, Università degli Studi di Firenze, Florence, Italy*
[3] *Dipartimento di Medicina e Oncologia Sperimentale, Università degli Studi di Torino, Turin, Italy*



In cellule stellate epatiche umane, la presenza di «ossidanti endogeni» (quelli che aumentano quando il fegato viene sottoposto ad iperattività)

- ***H_20_2***
- ***X/XO : xantine/xantine oxydase***
- ***DMNQ : dimethoxy naphtoquinone***

Determina l'aumento di radicali liberi (colore verde con luce UV)

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 30: 473-479, 2012

Silymarin suppresses hepatic stellate cell activation in a dietary rat model of non-alcoholic steatohepatitis: Analysis of isolated hepatic stellate cells

MINA KIM[1,2], SU-GEUN YANG[2], JOON MI KIM[3], JIN-WOO LEE[1], YOUNG SOO KIM[1] and JUNG IL LEE[1]

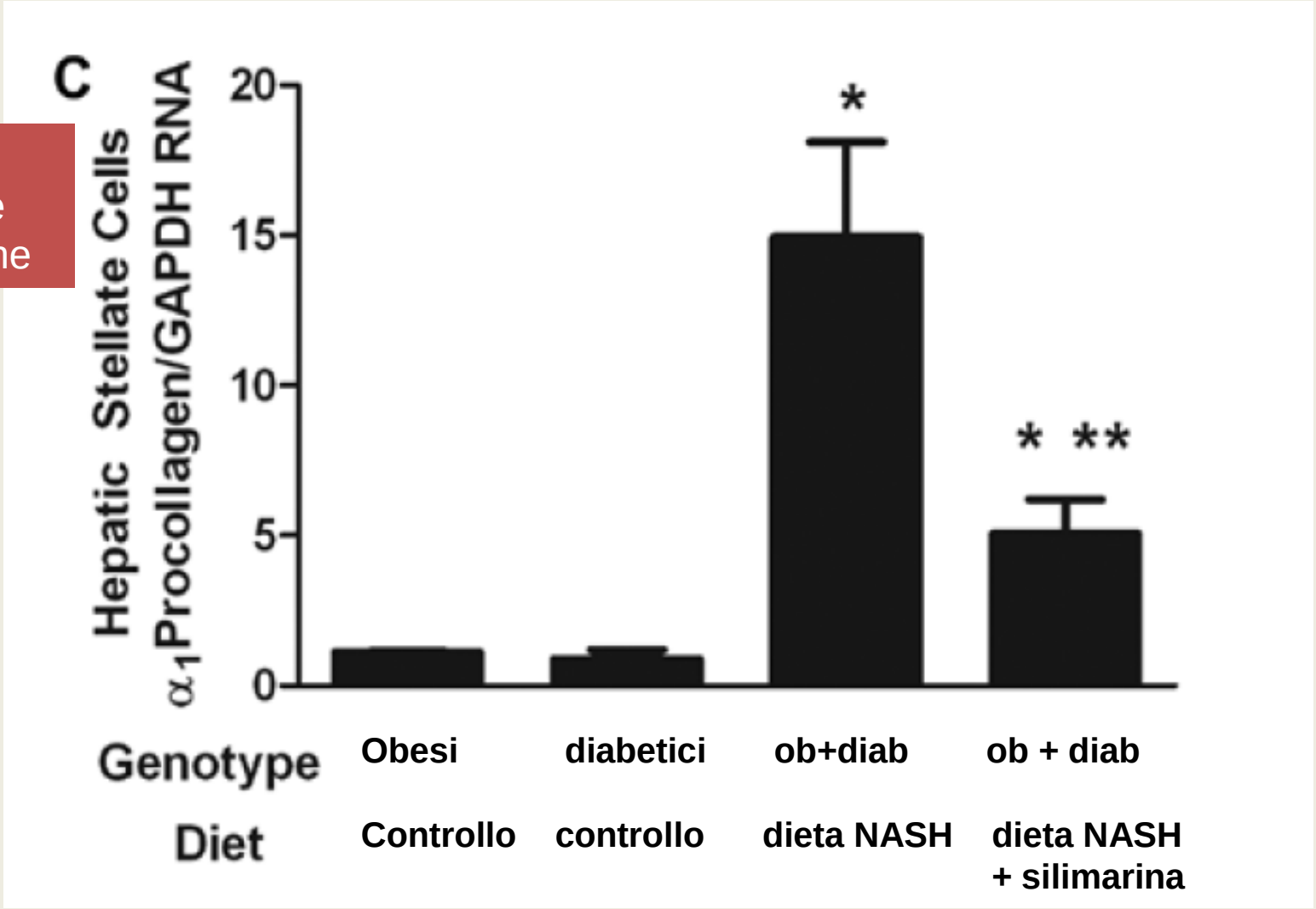
[1]Department of Internal Medicine, Division of Gastroenterology, Inha University School of Medicine, Jung-Gu, Incheon; [2]Utah-Inha DDS and Advanced Therapeutics Research Center, Yeonsu-Gu, Incheon; [3]Department of Pathology, Inha University School of Medicine, Jung-Gu, Incheon, Republic of Korea

Modello: dieta che causa uno stress ossidativo

Animali obesi e diabetici

MCD = methionin / choline deficient diet ± silymarin

Sintesi di collageno (fibrosi) da parte delle cellule stellate epatiche

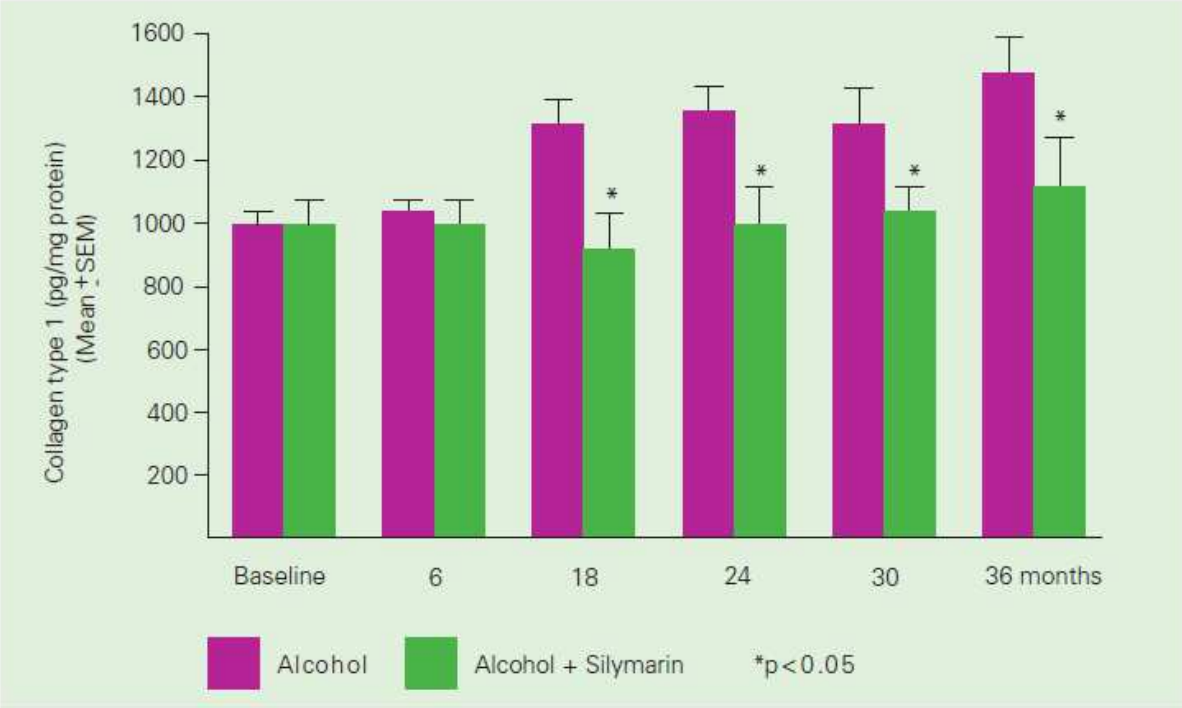


J Clin Gastroenterol • Volume 37, Number 4, October 2003

Silymarin Retards the Progression of Alcohol-Induced Hepatic Fibrosis in Baboons

Charles S. Lieber, MD, MACP, Maria A. Leo, MD, Qi Cao, MD, PhD, Chaoling Ren, MD, and Leonore M. DeCarli, BA

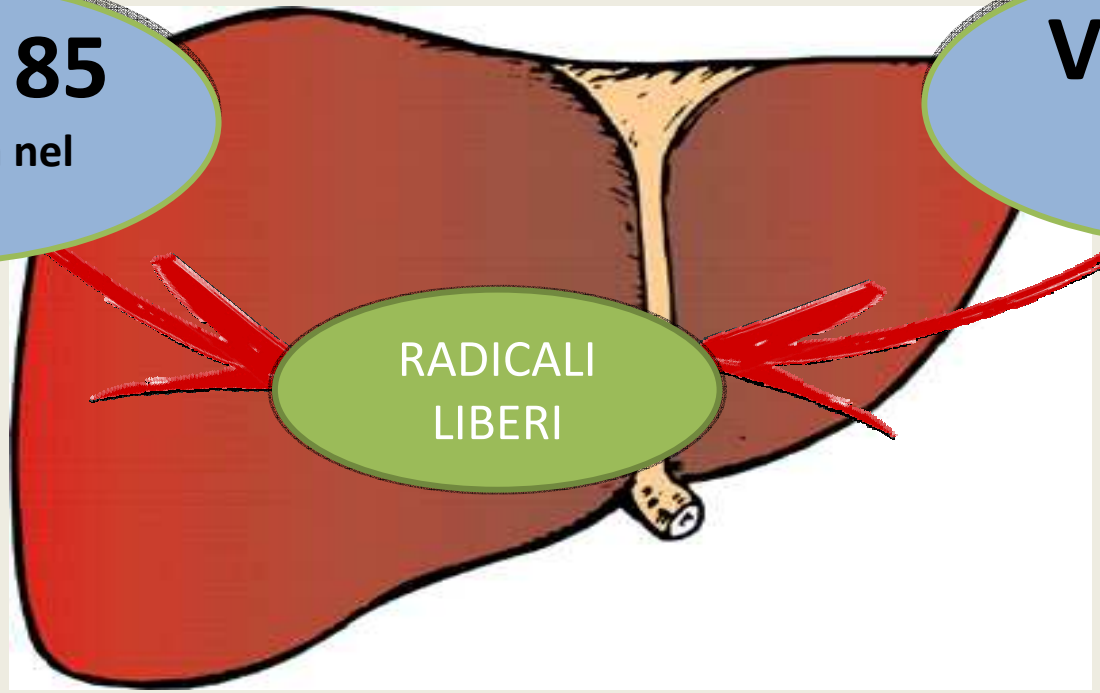
FIGURE 6.
Silymarin prevents accumulation of collagen I in alcohol-induced liver fibrosis in baboons.



Legalonplus®
Eurosil 85

Eurosil 85

Si concentra nel fegato



Vitamina E

Evidenze cliniche

90 pazienti esaminati, con ecografia epatica

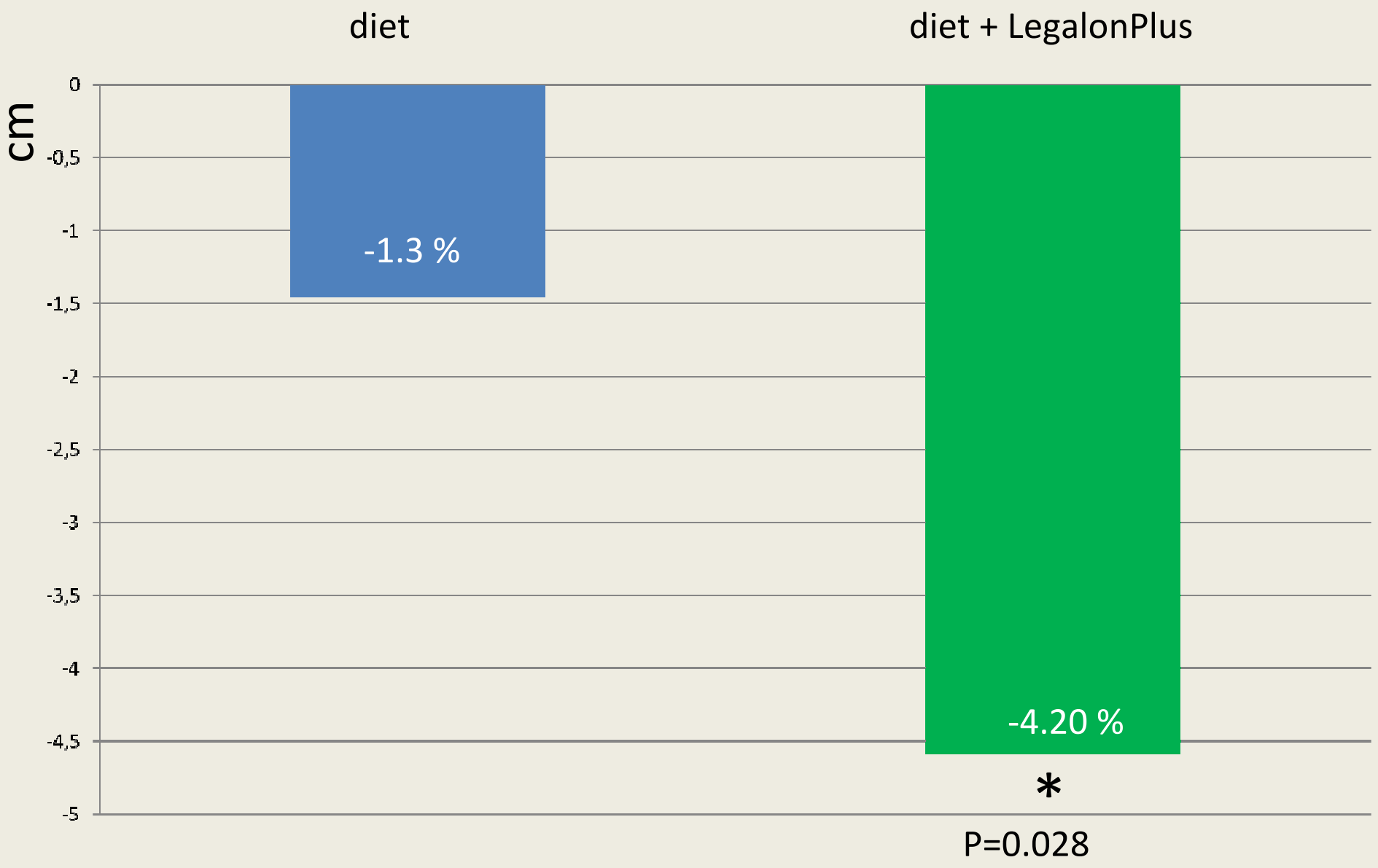
Sorrentino, De Stefano et al
-SED Valencia Giugno 2014 -publication submitted

Criteri Inclusione: steatosi almeno grado 1
sindrome metabolica (circonferenza TGL insulino-resistenza)

Criteri esclusione malattie epatiche virali acute e croniche
ostruzione vie biliari
consumo alcool > 20/40 gr giorno
farmaci per malattie epatiche

Parametro	Basale media pazienti
Lobo destro fegato	16.9 cm
ALT	32.15
AST	25.14
AST/ALT	0.88
GGT	38.33
TGL	174.18
glicemia	104.62
HB glicata	4.32%
Circonf addominale	107.22 cm
BMI	31.78

Reduction of abdominal circumference



Bedogni *et al. BMC Gastroenterology* 2010, **10**:98
http://www.biomedcentral.com/1471-230X/10/98

BMC Gastroenterology

RESEARCH ARTICLE Open Access

A simple index of lipid overaccumulation is a good marker of liver steatosis

LAP = (circonferenza – 65) x TGL mmol/l nel maschio
(circonferenza – 58) x TGL mmol/l nella femmina

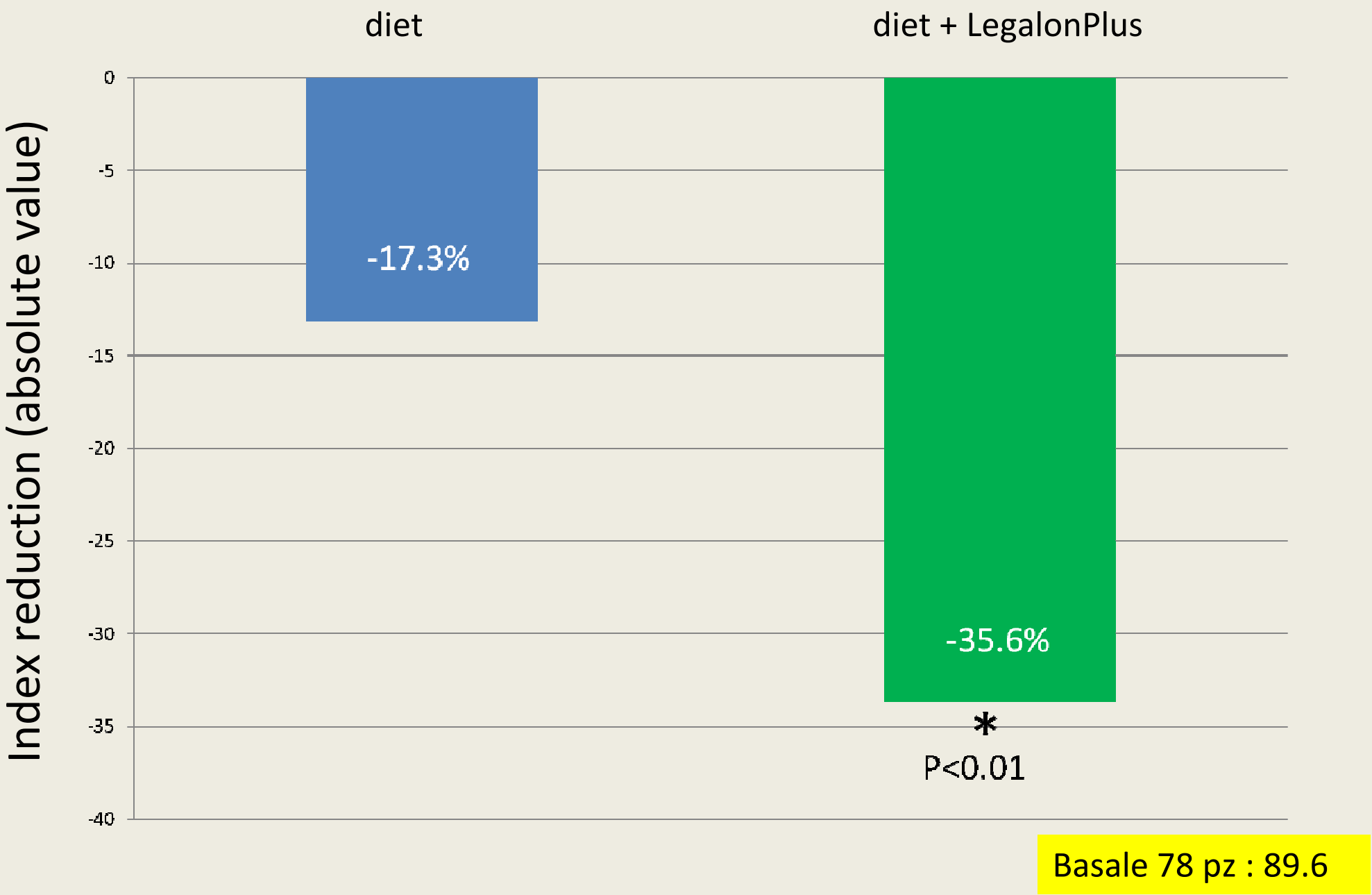
Giorgio Bedogni[1,2*], Henry S Kahn[3], Stefano Bellentani[4], Claudio Tiribelli[1]

Table 1 Measurements of the 588 study subjects.

	None *n* = 332, M = 167, F = 165			Intermediate *n* = 118, M = 79, F = 39			Severe *n* = 138, M = 101, F = 37			JT test
	p50	p25	p75	p50	p25	p75	p50	p25	p75	*p*-value
Age (years)	58	45	69	57	45	64	60	50	65	0.7
Ethanol (g/day)	9	0	27	9	0	28	16	2	43	0.006
Weight (kg)	69.5	61.5	76.5	78.7	71.0	89.0	83.4	75.5	93.2	<0.001
Height (m)	1.64	1.56	1.71	1.67	1.60	1.73	1.66	1.58	1.72	0.003
BMI (kg/m^2)	25.7	23.8	28.1	28.2	26.0	30.9	30.3	27.9	34.2	<0.001
Waist circumference (cm)	86.5	79.5	93.5	94.5	88.8	102.0	100.8	94.0	109.5	<0.001
ALT (U/L)	19	14	31	26	17	39	29	22	45	<0.001
AST (U/L)	21	17	26	21	18	28	24	20	30	<0.001
GGT (U/L)	18	13	27	27	17	43	36	23	61	<0.001
Glucose (mg/dl)	89	84	97	94	87	102	98	89	110	<0.001
Triglycerides (mg/dl)	90	65	123	115	88	162	149	98	205	<0.001
Total cholesterol (mg/dl)	211	183	236	212	184	238	216	184	244	0.2
LAP	24	15	39	43	27	62	63	36	93	<0.001
lnLAP	3.2	2.7	3.7	3.8	3.3	4.1	4.1	3.6	4.5	<0.001

Abbreviations: M = male; F = female; p50 = 50th percentile (median); p25 = 25th percentile (lower quartile); p75 = 75th percentile (upper quartile); JT test = Jonckerheere-Terpstra test for ordered alternatives (both ascending and descending); BMI = body mass index; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl-transferase; LAP = lipid accumulation product; lnLAP = natural logarithm of lipid accumulation product.

Reduction of LAP (Lipid Accumulation Product)



Basale 78 pz : 89.6

Parametro	Basale media pazienti
Lobo destro fegato	16.9 cm
ALT	32.15
AST	25.14
AST/ALT	0.88
GGT	38.33
TGL	174.18
glicemia	104.62
HB glicata	4.32%
Circonf addominale	107.22 cm
BMI	31.78

Rapporto AST/ALT

Angulo e Lindor, J. Gastroenterology and Hepatology 2004

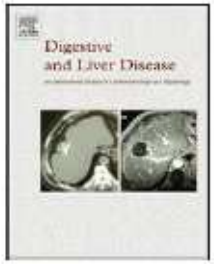
«la maggior parte dei pazienti con NAFLD hanno un rapporto AST/ALT < 1»

Digestive and Liver Disease 42 (2010) 503–508

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Liver, Pancreas and Biliary Tract

Hepatic steatosis index: A simple screening tool reflecting nonalcoholic fatty liver disease

Jeong-Hoon Lee[a], Donghee Kim[b,*], Hwa Jung Kim[c,d], Chang-Hoon Lee[e], Jong In Yang[b], Won Kim[e], Yoon Jun Kim[a], Jung-Hwan Yoon[a], Sang-Heon Cho[b], Myung-Whun Sung[b], Hyo-Suk Lee[a]

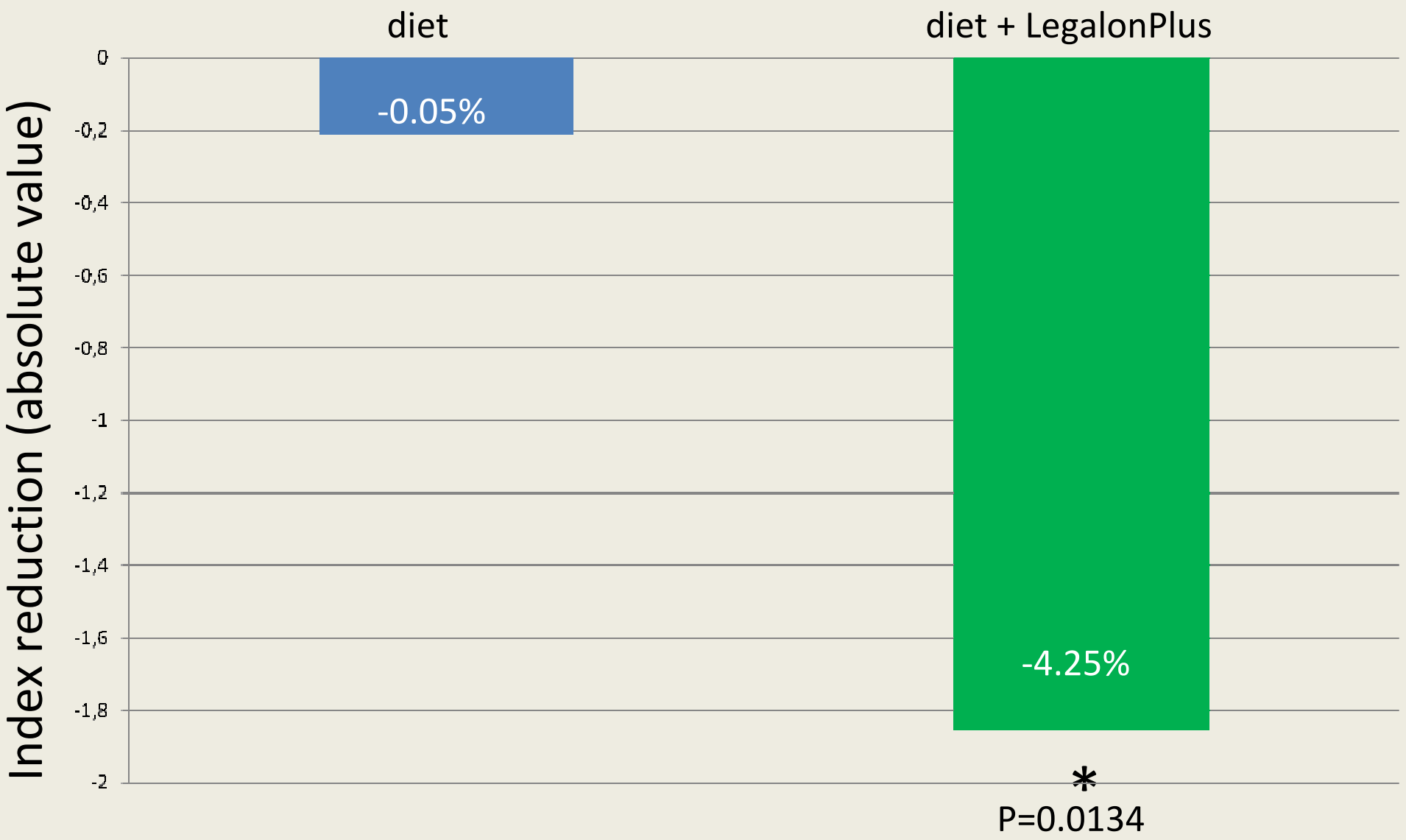
$$\text{hepatic steatosis index (HSI)} = 8 \times \text{ALT/AST ratio} + \text{BMI (+2, if DM; +2, if female)}$$

Validazione:

HSI had an area under receiver-operating curve of 0.812 (95% confidence interval, 0.801–0.824). At values of <30.0 or >36.0, HSI ruled out NAFLD with a sensitivity of 93.1%, or detected NAFLD with a specificity of 92.4%, respectively. Of 2692 subjects with HSI <30.0 or >36.0 in the derivation cohort, 2305 (85.6%) were correctly classified. HSI was validated in the subsequent validation cohort.

HSI < 30	93.1%	NON HA STEATOSI
HSI > 36	92.4%	HA STEATOSI

Reduction of HSI (Hepatic Steatosis Index)



Basale 78 pz. : 41.85

Parametro	Basale		variazione con dieta + LegalonPlus	variazione con dieta	

Parametro	Basale media pazienti
Lobo destro fegato	16.9 cm
ALT	32.15
AST	25.14
AST/ALT	0.88
GGT	38.33
TGL	174.18
glicemia	104.62
HB glicata	4.32%
Circonf addominale	107.22 cm
BMI	31.78

Grazie
per la cortese attenzione

Journal of Hepatology 1997; 26: 871-879
Printed in Denmark - All rights reserved
Munksgaard - Copenhagen

Journal of Hepatology
ISSN 0168-8278

Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients

Mario Velussi[1], Anna Maria Cernigoi[1], Ariella De Monte[1], Francesco Dapas[1], Cristina Caffau[2] and Mario Zilli[2]

[1] *Anti-Diabetes Centre and* [2]*Central Analysis Laboratory Monfalcone Hospital. Gorizia. Italy*

Cirrosi in pazienti diabetici

RISULTATI

- **Riduzione significativa (p<0.01) nella glicemia a digiuno già dopo 4 mesi.**
- **Riduzione significativa (p<0.01) del dosaggio di insulina necessario**

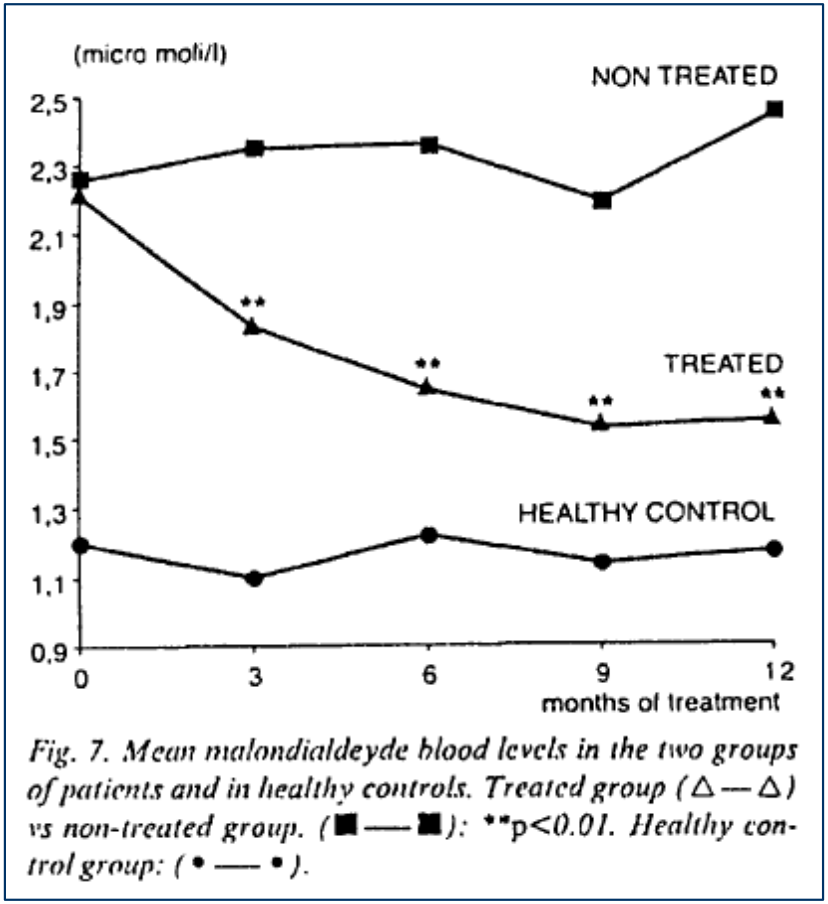


*Fig. 7. Mean malondialdeyde blood levels in the two groups of patients and in healthy controls. Treated group (△—△) vs non-treated group. (■—■): **p<0.01. Healthy control group: (•—•).*

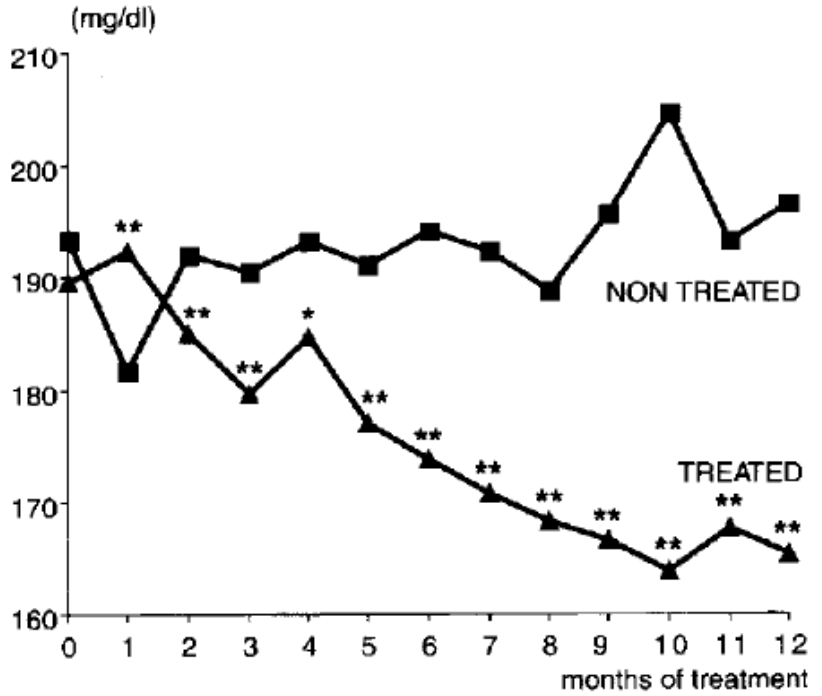


*Fig. 1. Mean fasting blood glucose in the two groups of patients. Treated group (△—△) vs non-treated group (■---■): *p<0.05; **p<0.01.*

LIPO-PEROSSIDAZIONE

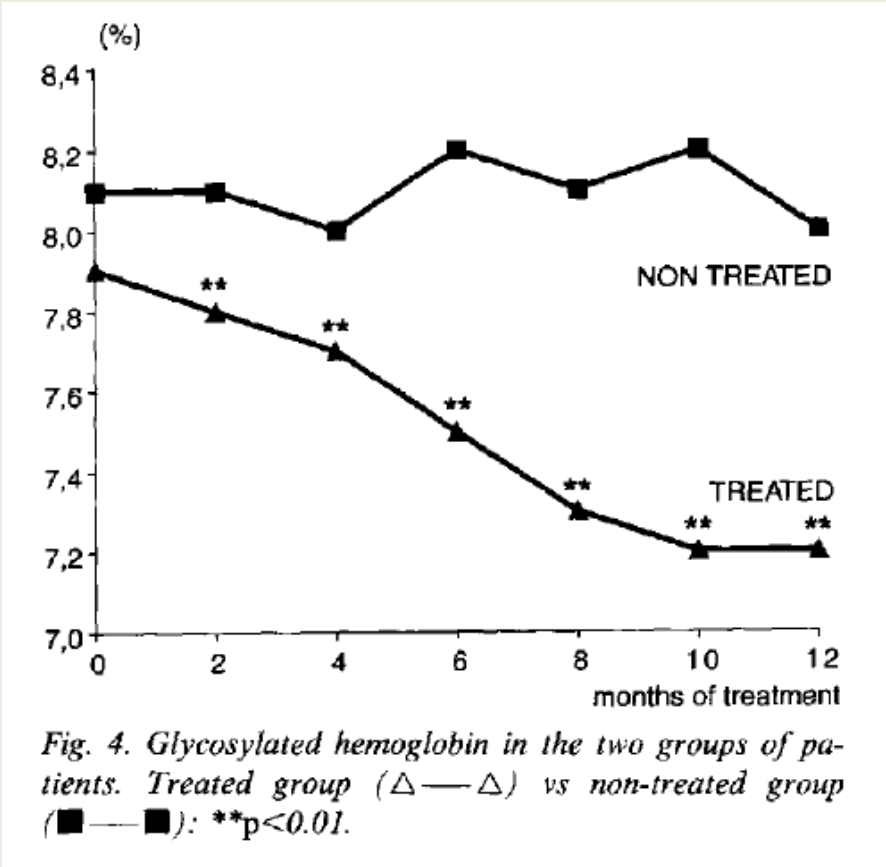


*Fig. 4. Glycosylated hemoglobin in the two groups of patients. Treated group (△——△) vs non-treated group (■——■): **p<0.01.*

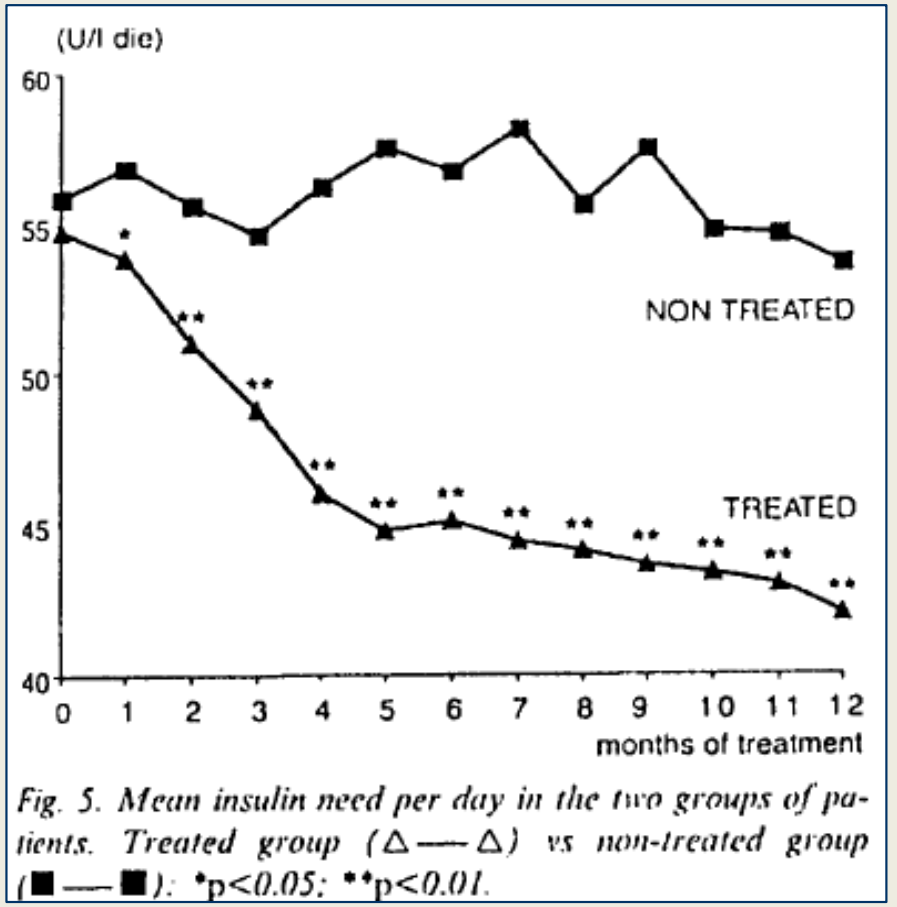


*Fig. 5. Mean insulin need per day in the two groups of patients. Treated group (△——△) vs non-treated group (■——■): *p<0.05; **p<0.01.*