Διατροφικές προκλήσεις στην αλκοολική ηπατοπάθεια

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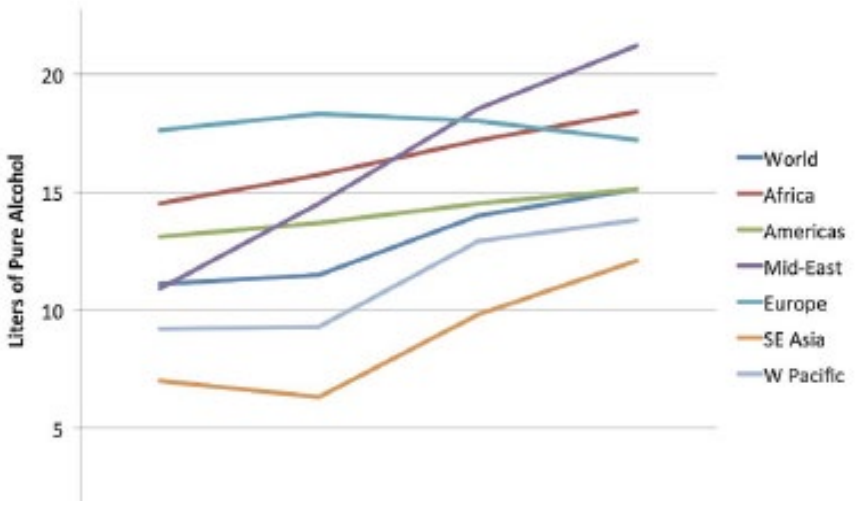
Epidemiology of Alcohol consumption

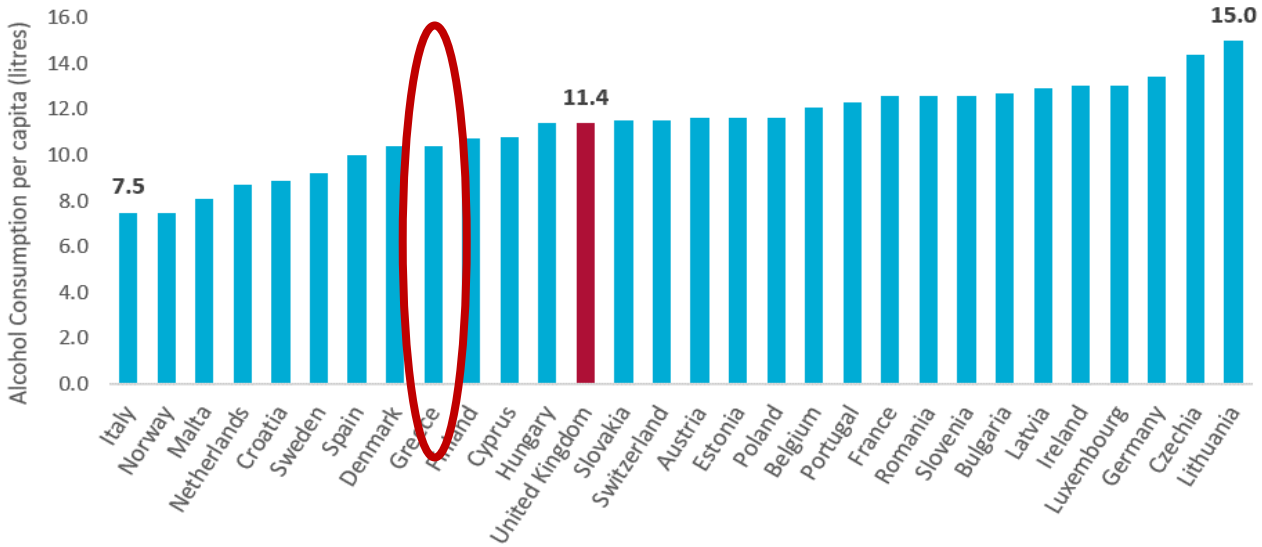
Trends in per capita consumption of alcohol (in liters of pure alcohol per year) among active drinkers. WHO 2018



Source: WHO (2018) *World status report on alcohol and health 2018*

Alcohol, total per capita (15+) consumption (in litres of pure a with 95%CI[i]

Country	Year	Both sexes	Male	Fema
Gabon	2016	11.5 [11.1-11.8]	18.1 [17.5-18.7]	4.6
	2010	10.7 [10.3-11.1]	16.8 [16.3-17.4]	4.4
Gambia	2016	3.8 [3.6-3.9]	6.6 [6.3-6.9]	1.
	2010	3.8 [3.7-4]	6.6 [6.4-6.9]	1.2
Georgia	2016	9.8 [9.4-10.2]	17.7 [17-18.4]	2.
	2010	10.4 [10-10.8]	18.6 [17.9-19.3]	3.3
Germany	2016	13.4 [13-13.7]	21.3 [20.7-21.8]	5.9
	2010	13 [12.7-13.2]	20.6 [20.1-21]	5.7
Ghana	2016	2.7 [2.5-2.8]	4.7 [4.4-4.9]	0.7
	2010	5.3 [4.9-5.6]	9.1 [8.5-9.7]	1.7
Greece	2016	10.4 [9.9-11]	17.2 [16.3-18.1]	4.1
	2010	10.4 [10.1-10.8]	16.9 [16.3-17.5]	4.3
	2016	9.3 [9-9.6]	14.9-15.9]	3.



*Clin **Liver** Dis (Hoboken). 2019 May 31;13(5):136-139.*

Drinking Levels Defined

- According to the ‘’Dietary Guidelines for Americans 2015-2020’’ US Department of Health and Human Services and US Department of Agriculture , **moderate drinking is up to 1 standard drink per day for women and up to 2 standard drinks per day for men.**

- NIAAA guidelines for limits on drinking apply to general populations rather than patients with ALD (i.e., **there is no known safe level of alcohol consumption for patients with ALD**).

Am J Gastroenterol 2018; 113:175–194

Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life

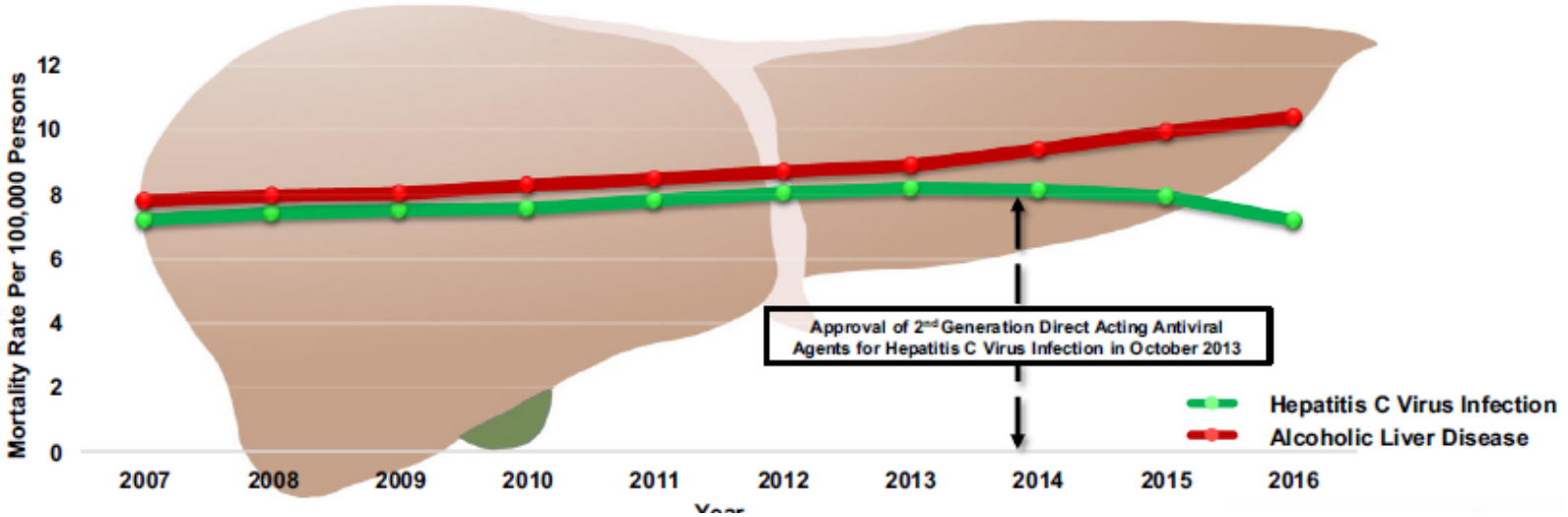
- 43,000 Swedish men
- 18-20 years old
- 40 years of follow-up

Η κατανάλωση του αλκοόλ στα πρώτα νεανικά χρόνια αποτελεί έναν σημαντικό παράγοντα εμφάνισης ηπατοπάθειας στη μετέπειτα ζωή

J Hepatol 2018 Mar;68(3):505-510.

Trends in Mortality Rates of Chronic Liver Diseases

- Alcoholic-Associated Liver Disease represents an estimated 3.8%of global mortality
- Death rate from cirrhosis was 12.0 per 100,000 persons
- Death rate from ALD-related cirrhosis was 5.7 per 100,000 persons



Gastrenterology 2018,155(4):1154-1163

Alcohol-associated liver disease (ALD)

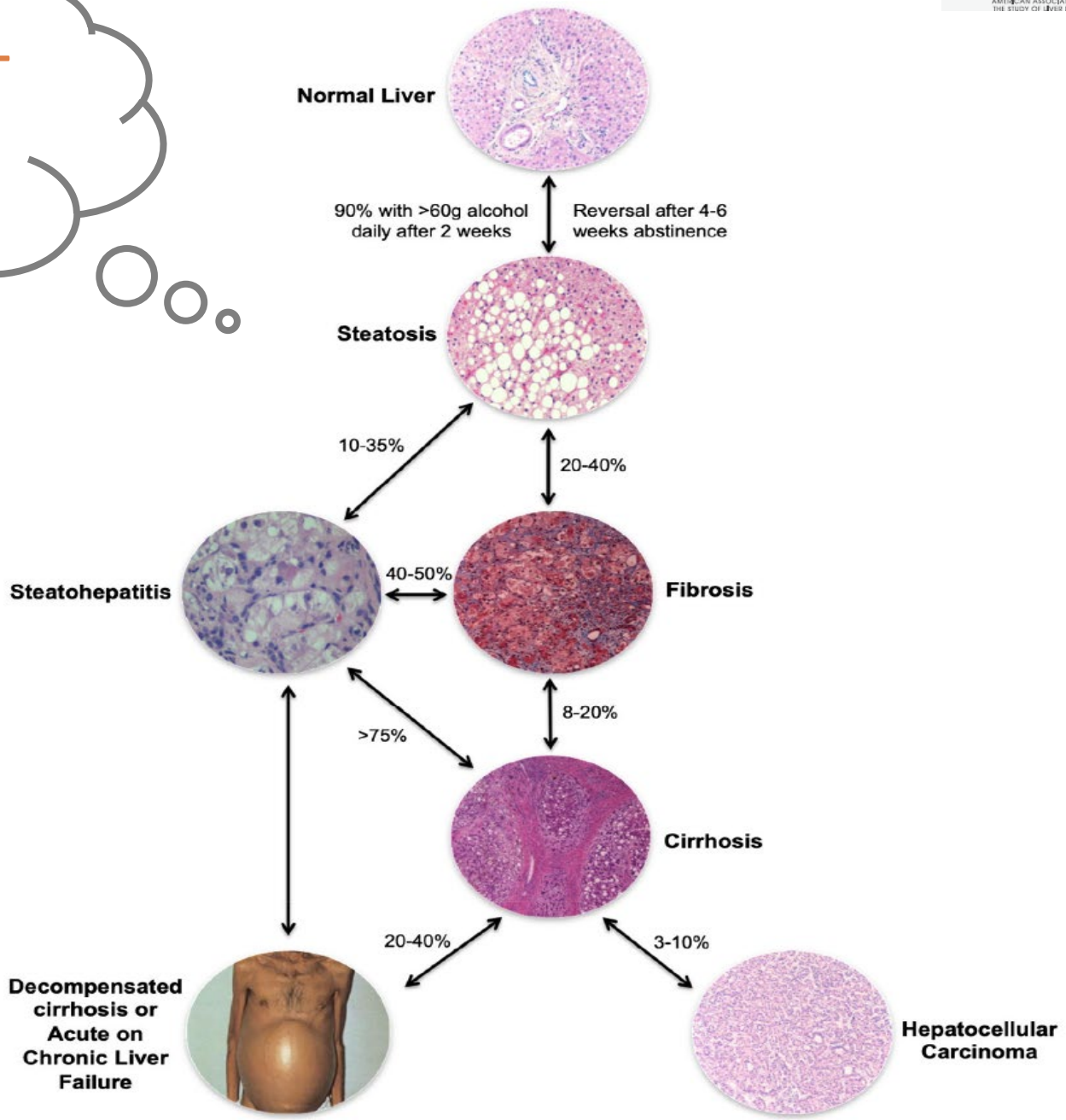
- Alcohol-associated liver disease (ALD) represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcoholic hepatitis (AH), alcohol-associated cirrhosis (AC), and acute AH presenting as acute-on chronic liver failure

It is increasingly recognized by providers that patients and their families seek to reduce the stigma of ALD, and a change from the term "*alcoholic*" **to "alcohol-associated"** will help

Categories of *alcohol abuse and dependence* have been replaced by the term **"alcohol use disorder,"** characterized as mild, moderate, or severe based on the accumulation of negative consequences and symptoms

Hepatology 2020,71(1):306-333

Alcohol=Alcohol-Associated Liver Disease ?

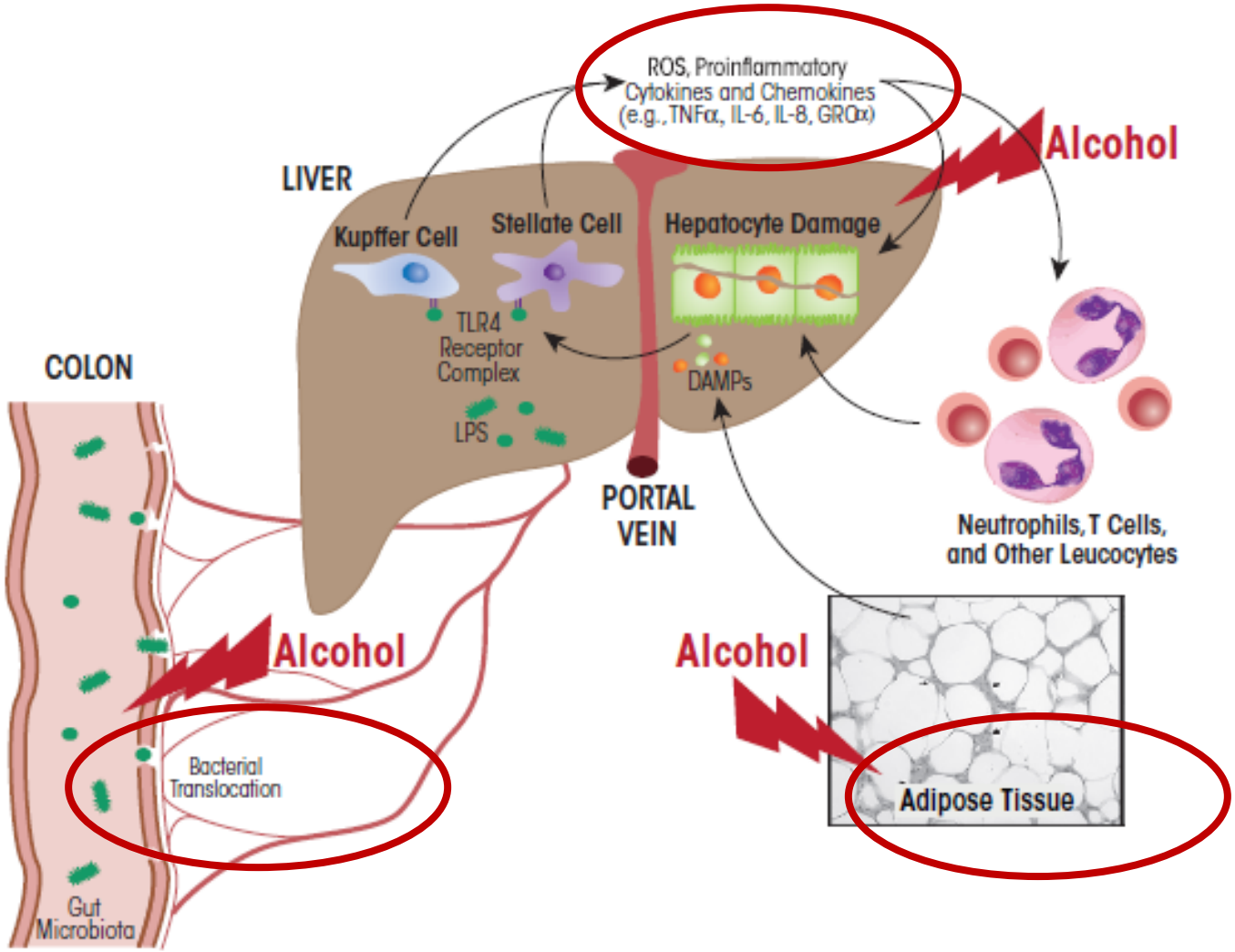


Hepatology 2020,71(1):306-333

Factors Affecting the Risk of Alcohol-Associated Liver Disease

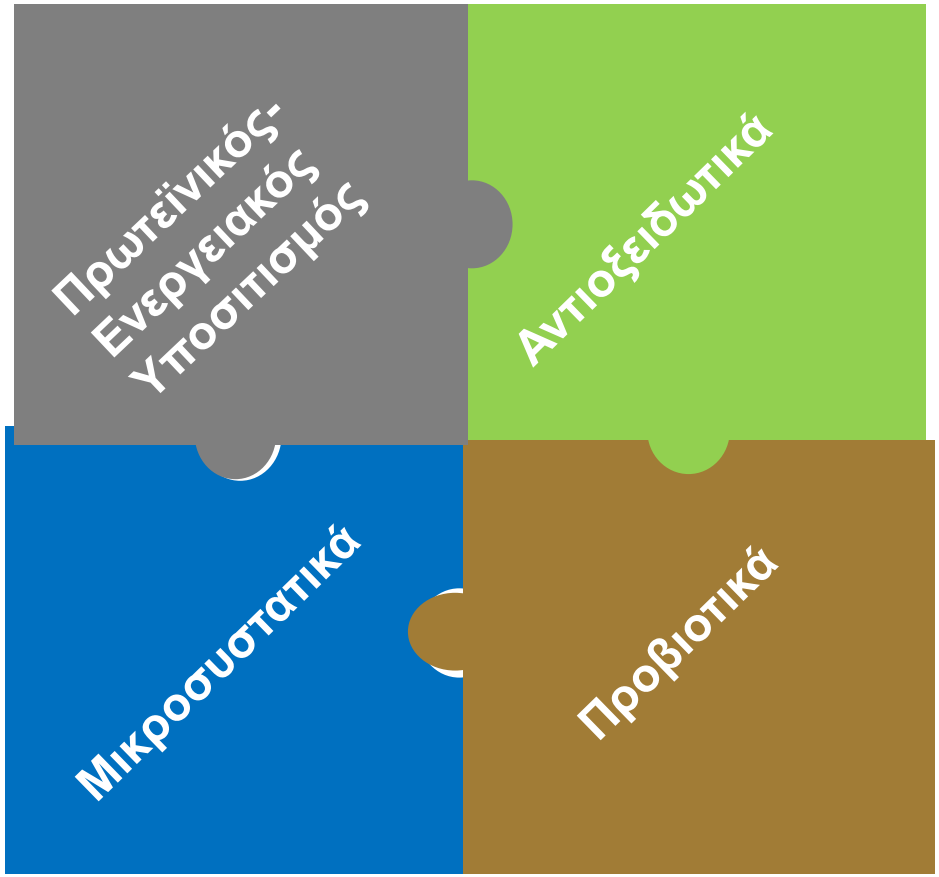
- Alcohol dose above threshold of 1 drink/day (women), 2 drinks/day (men)
- Pattern of consumption: daily drinking; drinking while fasting, binge drinking
- Smoking cigarettes
- Women compared with men
- Genetics*: PNPLA3, TM6SF2, MBOAT7, HSD17B13
- Increased BMI
- Presence of comorbid conditions: chronic viral hepatitis, hemochromatosis,
- NAFLD, NASH

Mechanisms in Alcohol-Associated liver disease



Alcohol Res. 2017, 38(2):147-161

Διατροφικές Προκλήσεις στην Ηπατοπάθεια σχετιζόμενη με το Αλκοόλ



VA cooperative study on alcoholic hepatitis II: prognostic significance of protein-calorie malnutrition[1,2]

CL Mendenhall, MD, PhD, T Tosch, PhD, RE Weesner, MD, P Garcia-Pont, MD, SJ Goldberg, MD, T Kiernan, MD, LB Seeff, MD, M Sorrell, MD, C Tamburro, MD, R Zetterman, MD, A Chedid, MD, T Chen, MD, and L Rabin, MD

ABSTRACT Three hundred and fifty-two patients with alcoholic hepatitis were evaluated for protein-calorie malnutrition (PCM). In order to facilitate data analysis of nutritional status, a PCM score was calculated for each patient using eight nutritional parameters. The PCM score correlated significantly with mortality, clinical severity of the liver disease, and biochemical liver dysfunction. When 30 day changes in the PCM scores were compared with 30 day caloric intake (expressed as percent basal energy expenditure (BEE)), a marginally significant correlation was observed ($p = 0.05$). However, those patients who showed improvement in their PCM score over 30 days of hospitalization also improved their 6-mo and 1-yr survival. These data indicate that nutrition, as determined by the PCM score, has prognostic significance. Additional studies are needed to establish the beneficial role for vigorous protein-calorie nutritional therapy in the management of alcoholic hepatitis. *Am J Clin Nutr* 1986;43:213–218.

Prognostic Factors in Alcoholic Liver Disease.

American Journal of Gastroenterology 1991,86, 2, 210-216.

Chedid, Antonio; Mendenhall, Charles L.; Gartside, Peter; French, Samuel W.; Chen, Thomas; Rabin, Lionel

Prevalence of malnutrition in Alcohol-Associated liver disease

Author, Year	Patients	Setting	N	Method of Measurement	Key Findings
Mendenhall et al,[25] 1984	Alcohol abuse with alcoholic hepatitis	Inpatient	363	Visceral proteins, immune response to skin tests, creatinine–height index, percent of ideal body weight	100% of patients with liver disease, admitted for alcohol abuse with alcoholic hepatitis
Mendenhall et al,[22] 1995	Alcoholic hepatitis	Inpatient	536	Visceral proteins, immune response to skin tests, creatinine–height index, percent of ideal body weight, skin fold thickness, midarm muscle area, total lymphocyte count grip strength, CD4 count, CD4:CD8 ratio	100% of patients with clinical jaundice
Mendenhall et al,[22] 1995	Alcohol abuse without laboratory evidence of liver injury	Outpatient	43	Visceral proteins, immune response to skin tests, creatinine–height index, percent of ideal body weight, skin fold thickness, midarm muscle area, total lymphocyte count grip strength, CD4 count, CD4:CD8 ratio	62% of patients with alcohol abuse without liver injury had some findings of malnutrition
Singal et al,[23] 2013	Patients with alcoholic cirrhosis undergoing liver transplantation	Inpatient	261	Subjective global assessment	84% of patients undergoing liver transplantation.

Clin Liver Dis 23 (2019) 99–114

Methods to quantify malnutrition in Alcohol-Associated liver disease

Method	Strengths	Weaknesses
SGA	Low cost, easily performed at bedside	Subjective
Anthropometric measurements	Low cost, easily performed at bedside	Potential for inaccuracy if edema present
Visceral proteins	Physician familiarity, simple blood test	Decreased liver synthetic function, use of IV albumin limits accuracy
Handgrip strength	Accurate, objective, easily performed at bedside	
BMI	Low cost, data readily available	Potential inaccuracy if edema present
Dry BMI	Low cost, data readily available	Potential inaccuracy if edema present

- The RFH-NPT is a screening tool for malnutrition in liver disease patients.
- Handgrip strength is a good predictor of the rate of complications within the next year but is an insensitive measure of fatigue (ESPEN 2019)

Clin Liver Dis 23 (2019) 99–114

Nutritional supplementation for management of hospitalized alcoholic hepatitis

- Meta analysis comparing nutritional supplementation plus a normal hospital diet versus diet alone.
- 7 studies, 124 control, 138 patients
- A limitation of the study is the fact that studies included either enteral or parenteral nutritional support compared with a normal hospital diet

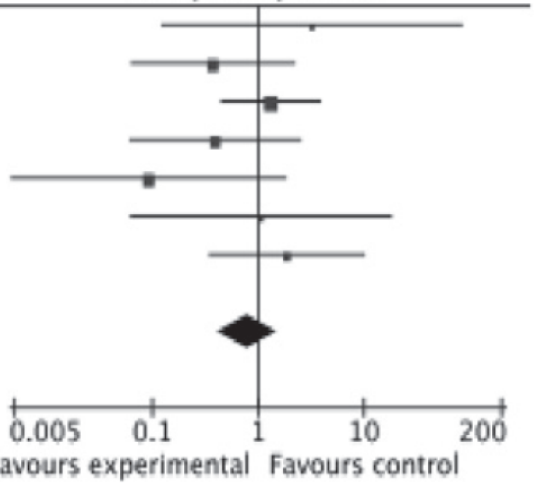
Nutritional supplementation versus hospital diet
- No mortality benefit
- No significantly improvements of biochemical parameters

Oral

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Anchord	1	14	0	14	2.1%	3.22 [0.12, 86.09]
Bunout	2	17	5	19	19.8%	0.37 [0.06, 2.25]
Calvey	16	42	7	22	27.0%	1.32 [0.44, 3.93]
Kearns	2	16	4	15	17.2%	0.39 [0.06, 2.55]
Nasrallah	0	17	4	18	20.2%	0.09 [0.00, 1.86]
Naveau	1	18	1	19	4.4%	1.06 [0.06, 18.30]
Simon	4	14	3	17	9.2%	1.87 [0.34, 10.25]
Total (95% CI)		**138**		**124**	**100.0%**	**0.80 [0.42, 1.52]**
Total events	26		24			

Heterogeneity: $Chi^2 = 5.71$, $df = 6$ ($P = 0.46$); $I^2 = 0\%$

Test for overall effect: $Z = 0.67$ ($P = 0.50$)



Can J Gastroenterol 2012;26(7):463-467

Cochrane Library

Cochrane Database of Systematic Reviews

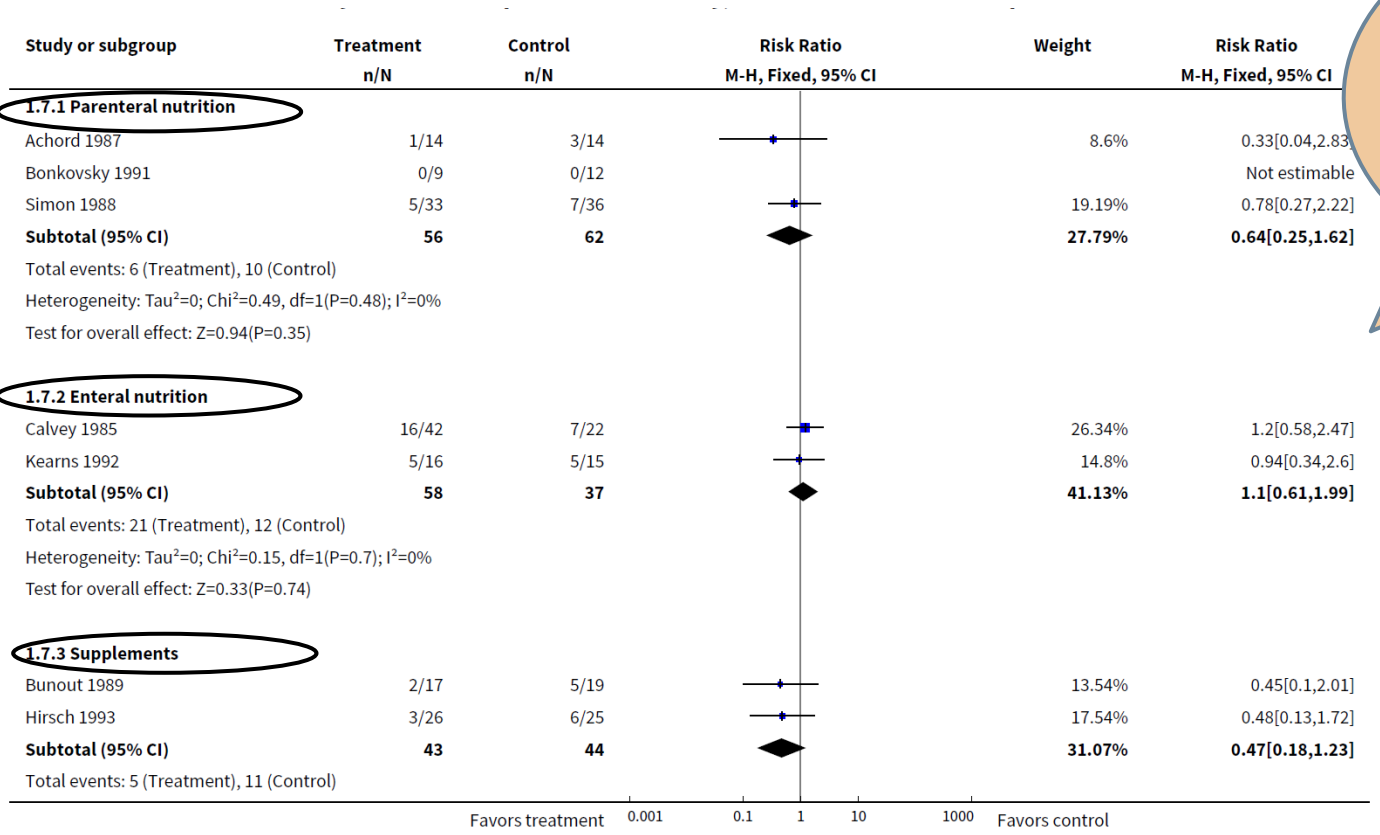
Nutritional support for liver disease (Review)

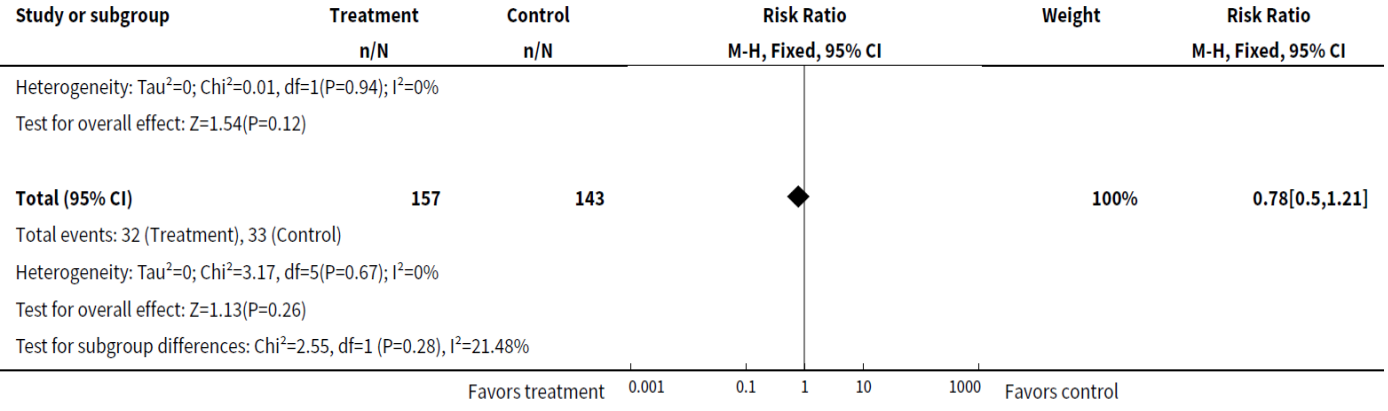
Koretz RL, Avenell A, Lipman TO

- 3 trials of parenteral nutrition,
- 2 trials of enteral nutrition
- 2 trials of oral nutritional supplements were conducted in patients with alcoholic hepatitis.
- Likewise, there were only a limited number of trials of supplements.
- In all of these trials, there were only a few significant differences.

.Cohrane Database Syst Rev 2012 May 16;(5)

Mortality in Alcoholic Hepatitis

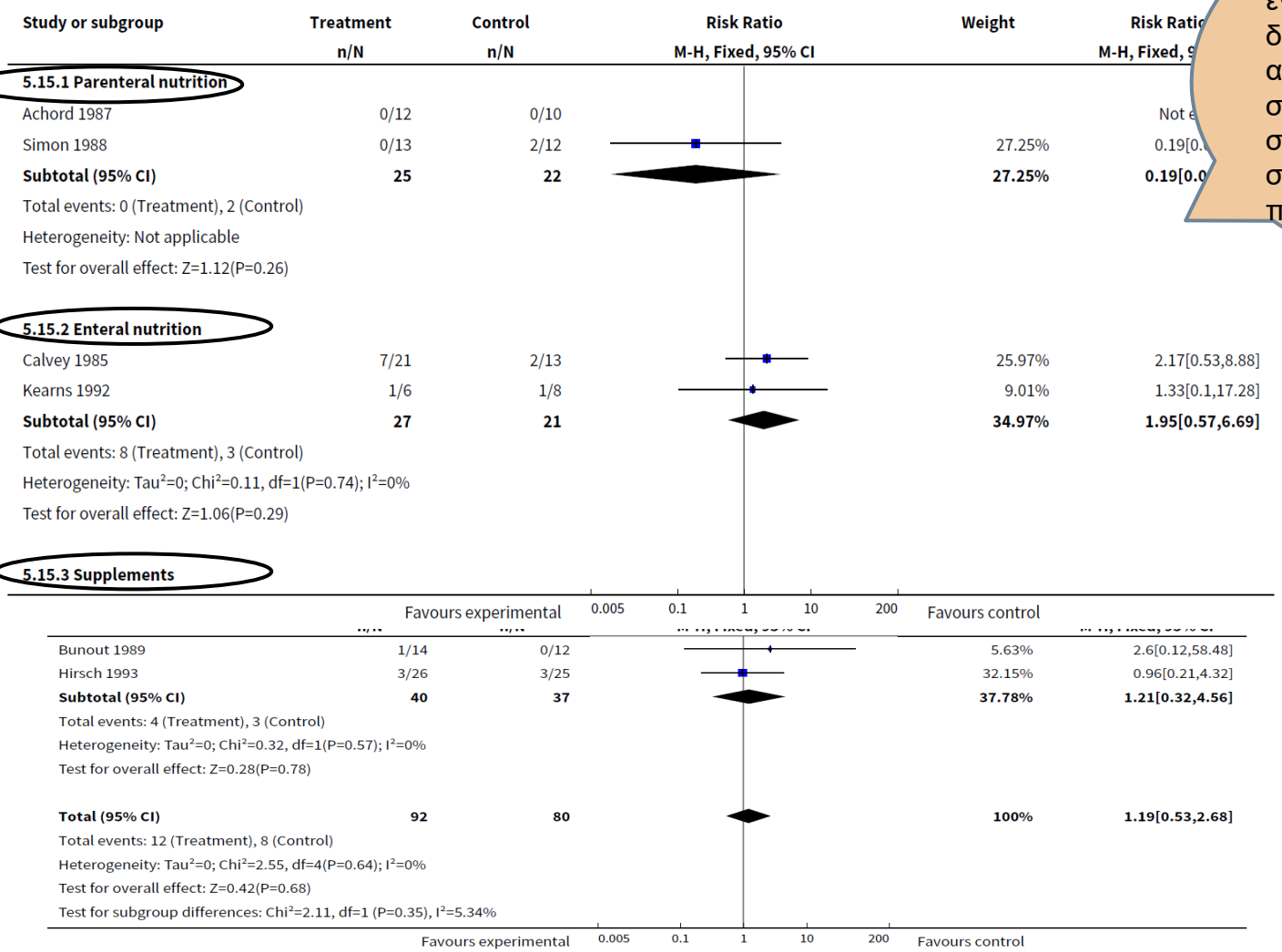




Η χορήγηση παρεντερικής εντερικής και συμπληρωμάτων διατροφής σε ασθενείς με αλκοολική ηπατίτιδα δεν έδωσε στατιστικά σημαντικές διαφορές στη θνησιμότητα συγκριτικά με τη μη διατροφική παρέμβαση

.Cochrane Database Syst Rev 2012 May 16;(5)

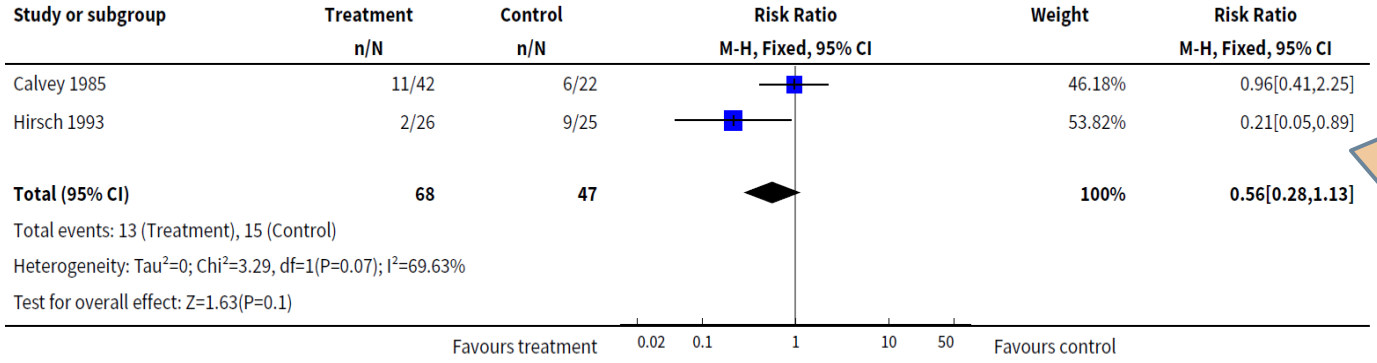
Appearance of encephalopathy in Alcoholic Hepatitis



Η χορήγηση παρεντερικής εντερικής και συμπληρωμάτων διατροφής σε ασθενείς με αλκοολική ηπατίτιδα δεν έδωσε στατιστικά σημαντικές διαφορές στην εμφάνιση εγκεφαλοπάθειας συγκριτικά με τη μη διατροφική παρέμβαση

.Cochrane Database Syst Rev 2012 May 16;(5)

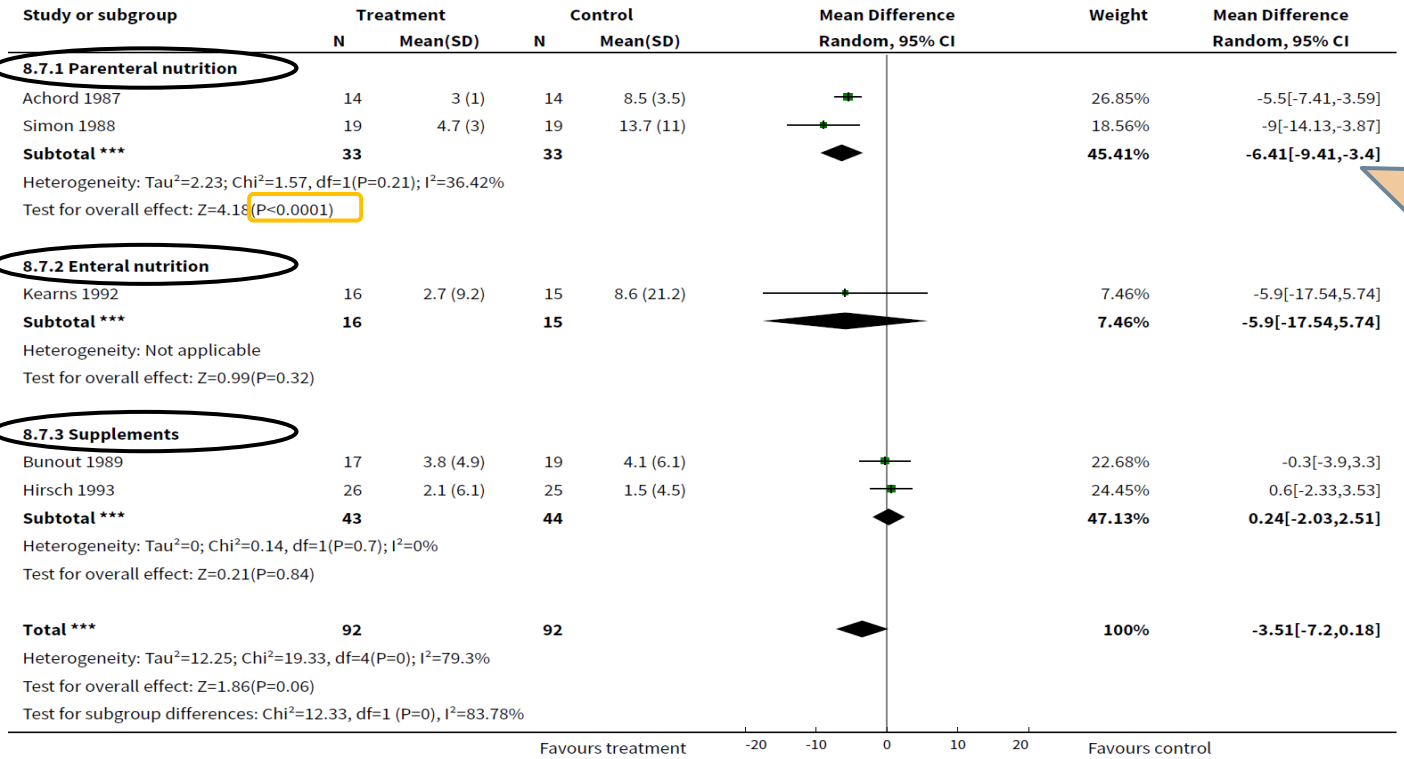
Infection in Alcoholic Hepatitis



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Calvey 1985	11/42	6/22		46.18%	0.96[0.41,2.25]
Hirsch 1993	2/26	9/25		53.82%	0.21[0.05,0.89]
Total (95% CI)	**68**	**47**		**100%**	**0.56[0.28,1.13]**
Total events: 13 (Treatment), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.29, df=1(P=0.07); I^2=69.63%					
Test for overall effect: Z=1.63(P=0.1)					

Η χορήγηση συμπληρωμάτων διατροφής σε ασθενείς με αλκοολική ηπατίτιδα δεν έδωσε στατιστικά σημαντικές διαφορές λοίμωξη συγκριτικά με τη μη διατροφική παρέμβαση

Serum Bilirubin in Alcoholic Hepatitis



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.7.1 Parenteral nutrition							
Achord 1987	14	3 (1)	14	8.5 (3.5)		26.85%	-5.5[-7.41,-3.59]
Simon 1988	19	4.7 (3)	19	13.7 (11)		18.56%	-9[-14.13,-3.87]
Subtotal ***	**33**		**33**			**45.41%**	**-6.41[-9.41,-3.4]**
Heterogeneity: Tau^2=2.23; Chi^2=1.57, df=1(P=0.21); I^2=36.42%							
Test for overall effect: Z=4.18(P<0.0001)							
8.7.2 Enteral nutrition							
Kearns 1992	16	2.7 (9.2)	15	8.6 (21.2)		7.46%	-5.9[-17.54,5.74]
Subtotal ***	**16**		**15**			**7.46%**	**-5.9[-17.54,5.74]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
8.7.3 Supplements							
Bunout 1989	17	3.8 (4.9)	19	4.1 (6.1)		22.68%	-0.3[-3.9,3.3]
Hirsch 1993	26	2.1 (6.1)	25	1.5 (4.5)		24.45%	0.6[-2.33,3.53]
Subtotal ***	**43**		**44**			**47.13%**	**0.24[-2.03,2.51]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=0.21(P=0.84)							
Total ***	**92**		**92**			**100%**	**-3.51[-7.2,0.18]**
Heterogeneity: Tau^2=12.25; Chi^2=19.33, df=4(P=0); I^2=79.3%							
Test for overall effect: Z=1.86(P=0.06)							
Test for subgroup differences: Chi^2=12.33, df=1 (P=0), I^2=83.78%							

Η χορήγηση παρεντερικής διατροφής σε ασθενείς με αλκοολική ηπατίτιδα έδωσε στατιστικά σημαντικές διαφορές στην χολερυθρίνη ορού συγκριτικά με τη μη διατροφική παρέμβαση

.Cochrane Database Syst Rev 2012 May 16;(5)

Nutritional therapy may have beneficial effects on clinical outcomes in cirrhosis and alcoholic hepatitis.

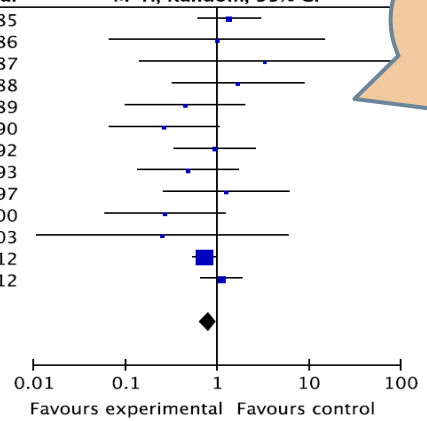
- 329 patients allocated to enteral (9 trials) or intravenous (4 trials) nutrition and 334 controls
- Diet attempted to fulfil at least 75% of the nutritional demands
- The nutritional interventions contained between 71 and 150 g of protein/day and 2115 to 4260 kcal/day.

Nutritional therapy vs. no intervention. Outcome; Mortality overall

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Calvey 1985	9	21	7	22	7.6%	1.35 [0.61, 2.96]	1985
Naveau 1986	1	20	1	20	0.6%	1.00 [0.07, 14.90]	1986
Achord 1987	1	19	0	21	0.5%	3.30 [0.14, 76.46]	1987
Simon 1988	3	16	2	18	1.7%	1.69 [0.32, 8.85]	1988
Bunout 1989	2	17	5	19	2.1%	0.45 [0.10, 2.01]	1989
Cabre 1990	2	16	9	19	2.5%	0.26 [0.07, 1.05]	1990
Kearns 1992	5	16	5	15	4.5%	0.94 [0.34, 2.60]	1992
Hirsch 1993	3	26	6	25	2.9%	0.48 [0.13, 1.72]	1993
De Ledinghen 1997	3	12	2	10	1.9%	1.25 [0.26, 6.07]	1997
Cornu 2000	2	42	7	40	2.1%	0.27 [0.06, 1.23]	2000
Hu 2003	0	40	1	30	0.5%	0.25 [0.01, 5.98]	2003
Sorrentino 2012	24	40	33	40	55.8%	0.73 [0.54, 0.97]	2012
Dupont 2012	17	44	19	55	17.4%	1.12 [0.66, 1.88]	2012
Total (95% CI)		**329**		**334**	**100.0%**	**0.80 [0.64, 0.99]**	
Total events	72		97				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 11.84$, df = 12 ($P = 0.46$); $I^2 = 0\%$

Test for overall effect: $Z = 2.02$ ($P = 0.04$)



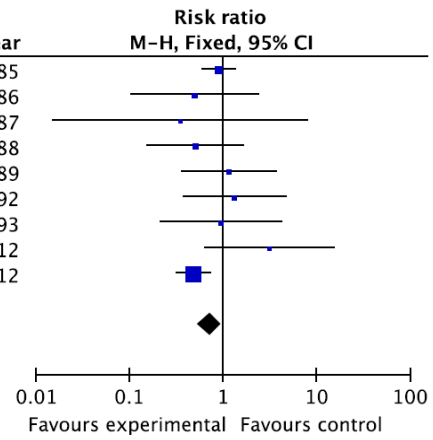
Η Διατροφική παρέμβαση μείωσε τη θνησιμότητα και την πιθανότητα εμφάνισης ηπατικής εγκεφαλοπάθειας

Nutritional therapy vs. no intervention. Outcome; hepatic encephalopathy

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
Calvey 1985	9	12	10	12	15.8%	0.90 [0.60, 1.36]	1985
Naveau 1986	2	20	4	20	6.3%	0.50 [0.10, 2.43]	1986
Achord 1987	0	19	1	20	2.3%	0.35 [0.02, 8.10]	1987
Simon 1988	3	13	5	11	8.5%	0.51 [0.16, 1.66]	1988
Bunout 1989	4	13	4	15	5.9%	1.15 [0.36, 3.72]	1989
Kearns 1992	4	12	3	12	4.7%	1.33 [0.38, 4.72]	1992
Hirsch 1993	3	23	3	22	4.8%	0.96 [0.22, 4.24]	1993
Dupont 2012	5	44	2	55	2.8%	3.13 [0.64, 15.34]	2012
Sorrentino 2012	15	40	31	40	48.9%	0.48 [0.31, 0.75]	2012
Total (95% CI)		**196**		**207**	**100.0%**	**0.73 [0.55, 0.96]**	
Total events	45		63				

Heterogeneity: $\chi^2 = 10.03$, df = 8 ($P = 0.26$); $I^2 = 20\%$

Test for overall effect: $Z = 2.21$ ($P = 0.03$)

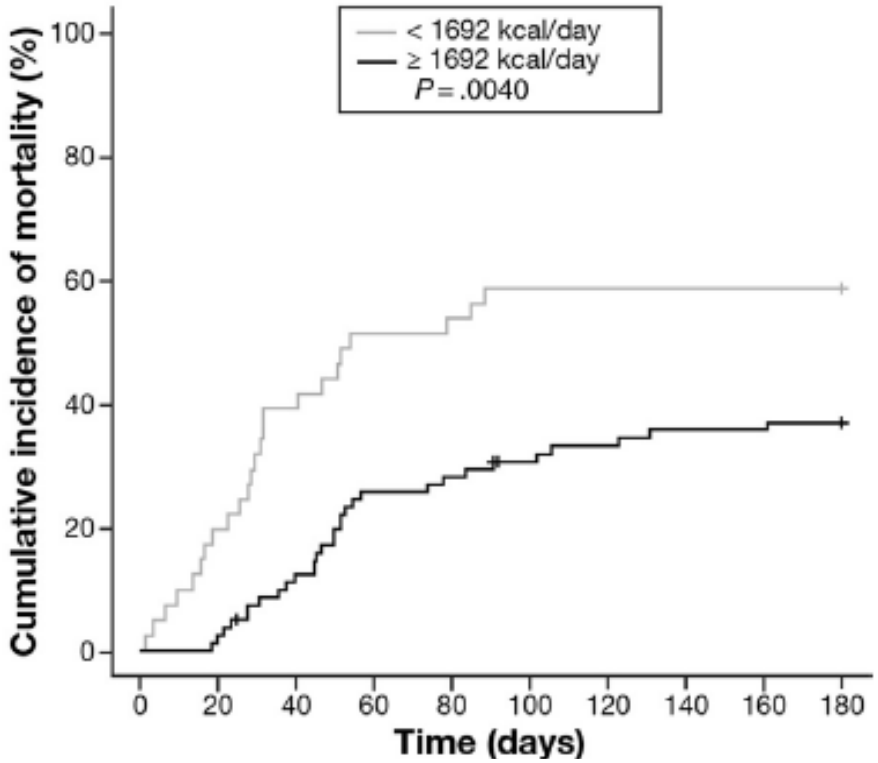


Liver Int. 2015; 35: 2072–2078

Enteral Nutrition in Alcoholic Hepatitis

- 136 patients
- Intensive enteral nutrition plus methylprednisolone or conventional nutrition plus methylprednisolone (controls).
- In the intensive enteral nutrition group, enteral nutrition was given via feeding tube for 14 days
- 1500 kcal/ day if BW was less than 60 kg, 2000 kcal/day if BW was between 60 and 90 kg, and 3000kcalL/day if BW was more than 90 kg plus oral nutritional intake..

Ενεργειακή πρόσληψη <21.5kcal/kg/day αύξησε στατιστικά σημαντικά τη θνησιμότητα στους 6 μήνες συγκριτικά με τη σίτιση με >21.5 kcal/kg/day



Gastroenterology 2016;150:903–910

Leucine enriched branched chain amino acid supplementation in Alcohol-Associated cirrhosis

Στόχος: Να προσδιοριστεί η επίδραση των BCAA στη μυϊκή μάζα των κιρρωτικών από αλκοόλ.

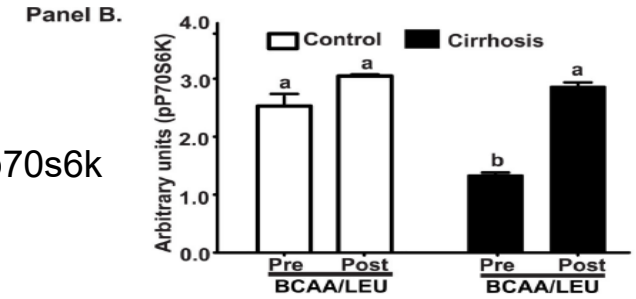
Μέθοδοι: Σε 6 κιρρωτικούς ασθενείς από αλκοόλ και 8 δείγματα ελέγχου από ,πήραν βιοψίες από μυ πριν και 7ώρες μετά τη χορήγηση από το στόμα BCAA εμπλουτισμένα με λευκίνη. Με ανοσοαποτύπωση προσδιόρισαν τις πρωτεΐνες που εμπλέκονται στην πρωτεϊνική σύνθεση και πρωτεΐνες που εμπλέκονται στην αυτοφαγία

Hepatology. 2015, 61(6): 2018–2029

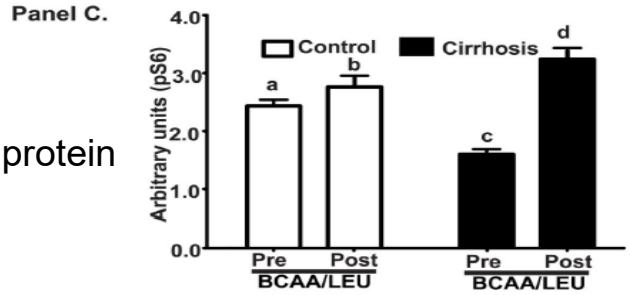
Leucine enriched branched chain amino acid supplementation in Alcohol-Associated cirrhosis

Regulating protein synthesis

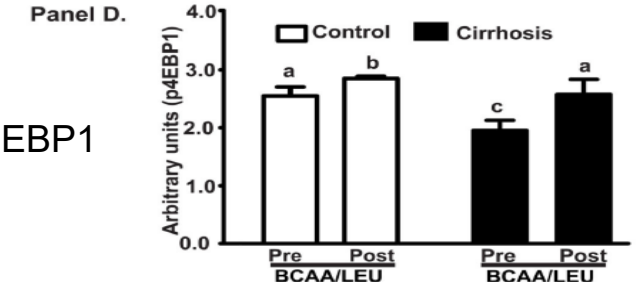
p70s6k



s6 protein

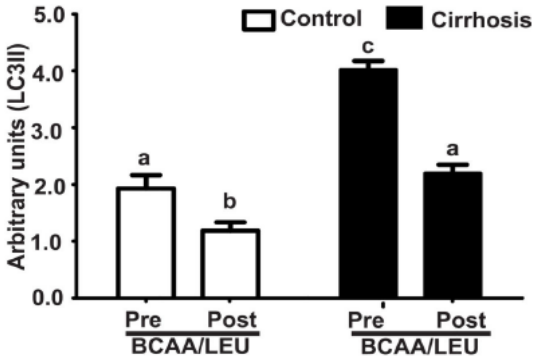


4EBP1

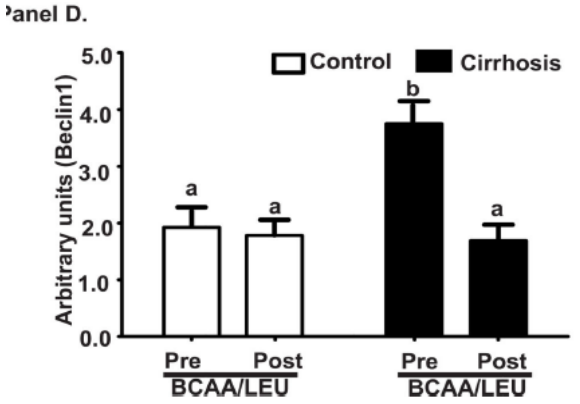


Proteolysis markers

LC3



Beclin1

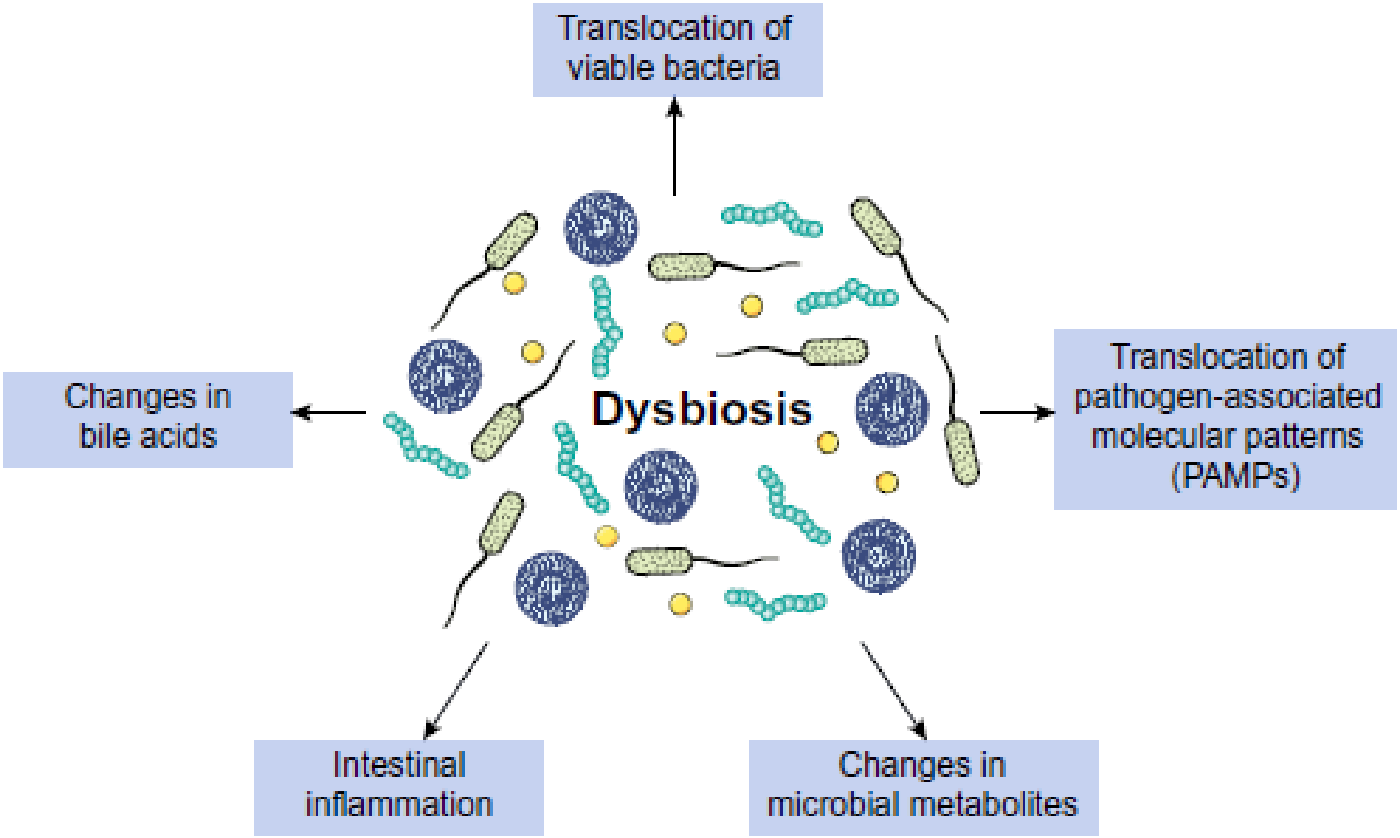


Η χορήγηση BCAA εμπλουτισμένα με λευκίνη
- Επάγουν την πρωτεϊνική σύνθεση
- Μειώνουν την πρωτεόλυση των μυϊκών πρωτεϊνών

Hepatology. 2015, 61(6): 2018–2029

Διατροφικές Προκλήσεις στην Ηπατοπάθεια σχετιζόμενη με το Αλκοόλ

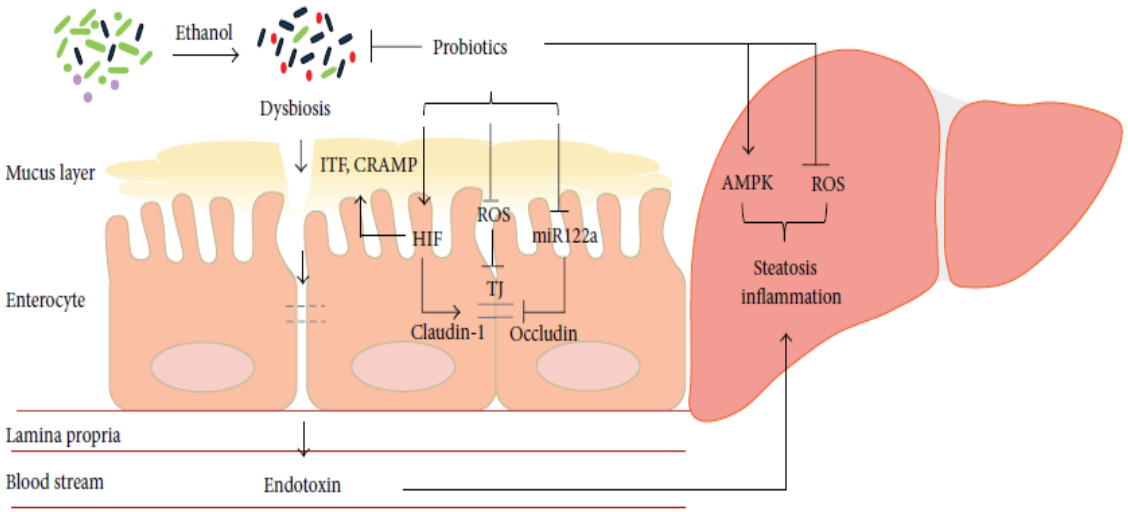
Contribution of the gut microbiota to alcohol-related liver disease



Journal of Hepatology 2019.70,260–272

Mechanisms of Probiotics in Improvement of Alcoholic Liver Injury

- Antioxidant Activity
- Improve Alcohol-Induced Lipid Metabolism
- Reduce Inflammatory Cytokine
- Enhance Intestinal Barrier Function and Modulate the Mucosal Immune System
- Regulate Intestinal Flora



.Gastrenterol Res Pract 2016;2016:5491465

Investigations into ALD and microbiota composition in humans

Study	Design and participant details	Microbial findings and summary of results
ALD without cirrhosis		
Mutlu et al. 2012 (REF.[9])	• Cohort study of stool and colonic mucosal microbiota with healthy controls ($n = 18$) • Patients with ALD without cirrhosis ($n = 28$) • Patients with alcoholic cirrhosis ($n = 19$)	Dysbiosis with lower Bacteroidetes and higher Proteobacteria seen in selected individuals with alcoholism, which was linked with endotoxin
Leclercq et al. 2014 (REF.[58])	• Longitudinal study of stool microbiota before and after 3 weeks of abstinence • Patients with F0 or F1 liver disease ($n = 60$)	A selected group had increased intestinal permeability and dysbiosis associated with lower abundance of Ruminococcaceae taxa, which reversed after abstinence
Alcoholic cirrhosis with abstinence		
Chen et al. 2011 (REF.[104])	• Cross-sectional analysis of microbiota • Outpatients with cirrhosis of multiple aetiologies ($n = 12$ with ALD)	Dysbiosis was similar in different aetiologies
Bajaj et al. 2012 (REF.[65])	• Cross-sectional analysis of cognition and gut microbiota • Patients with cirrhosis and HE ($n = 17$) with ALD alone in 13 patients and ALD and with hepatitis C in 8 patients	HE rather than alcoholic aetiology was the determinant of dysbiosis and cognitive impairment
Bajaj et al. 2014 (REF.[52])	• Cross-sectional and longitudinal studies • Patients with cirrhosis ($n = 219$ in total, $n = 43$ with ALD and $n = 32$ with NASH)	Patients with ALD-related cirrhosis had worse dysbiosis than those without ALD despite abstinence and similar cirrhosis severity
Kakiyama et al. 2013 (REF.[105])	Cross-sectional study of microbiota and faecal bile acids in 47 patients with cirrhosis (7 with ALD-related cirrhosis)	Dysbiosis and bile acid profiles were similar in different aetiologies
Alcoholic cirrhosis with active drinking		
Kakiyama et al. 2014 (REF.[53])	• Analysis of secondary bile acids • Healthy controls ($n = 19$) • Actively drinking individuals without cirrhosis ($n = 6$) • Patients with cirrhosis ($n = 78$, of whom $n = 10$ were actively drinking, $n = 38$ were abstinent and $n = 30$ had cirrhosis unrelated to alcohol)	Regardless of cirrhosis status, secondary bile acid levels were higher in the serum and stool of active drinkers and lower in non-drinkers
Tuomisto et al. 2014 (REF.[68])	• Autopsy study of liver microbiota • Patients with alcoholism and cirrhosis ($n = 13$) • Patients with alcoholism without cirrhosis ($n = 15$) • Control individuals without alcoholism ($n = 14$) • A group of living individuals was also recruited • Healthy control individuals ($n = 7$) • Patients with alcoholism and cirrhosis ($n = 12$)	Sterility of the liver was lowest in patients with alcoholic cirrhosis
Dubinkina et al. 2017 (REF.[61])	• Cross-sectional metagenomic analysis of stool microbiota and functional capacity • Patients with alcohol dependence and cirrhosis ($n = 27$) • Patients with alcohol dependence without cirrhosis ($n = 72$)	Commensal bacteria were depleted in both groups but increases in *Lactobacillus* spp. and *Bifidobacterium* spp. and oral microbiota were seen in patients with cirrhosis. Functional microbiota pathways related to alcohol metabolism and inflammation were upregulated in those with cirrhosis
Bajaj et al. 2017 (REF.[51])	• Stool, duodenal, ileal and colonic microbiota analysis; duodenal and faecal bile acid profile and stool metabolomics • Healthy control individuals ($n = 34$) • Actively drinking patients with cirrhosis ($n = 37$) • Abstinent patients with cirrhosis ($n = 68$)	Dysbiosis was prevalent in all tissues studied in actively drinking patients with cirrhosis. Higher secondary bile acid levels were seen in both duodenal fluid and stool, with greater concentration of metabolites in the stool in actively drinking patients with cirrhosis
Alcoholic hepatitis		
Llopis et al. 2016 (REF.[69])	• Stool microbiota analysis • Patients without alcoholic hepatitis ($n = 16$) • Patients with non-severe alcoholic hepatitis ($n = 12$) • Patients with severe alcoholic hepatitis ($n = 10$)	Levels of streptococci, enterobacteria and bifidobacteria were higher in severe alcoholic hepatitis than in other patient groups. Bilirubin concentrations were positively linked with levels of enterobacteria and negatively linked with levels of clostridial taxa
Grander et al. 2017 (REF.[70])	• Analysis of *A. muciniphila* levels in stool samples • Healthy control individuals ($n = 16$) • Patients with non-severe alcoholic hepatitis ($n = 21$) • Patients with severe alcoholic hepatitis ($n = 15$)	*A. muciniphila* abundance reduced with increasing severity of ALD and was lowest in alcoholic hepatitis
Puri et al. 2017 (REF.[73])	• Analysis of circulating microbiota and inferred functionality • Non-drinking control individuals ($n = 20$) • Active drinkers without liver disease ($n = 19$) and patients with moderate alcoholic hepatitis ($n = 18$) • Patients with severe alcoholic hepatitis ($n = 19$)	Increased levels of circulating 16S rRNA in both alcoholic hepatitis groups. Patients with severe alcoholic hepatitis had the worst endotoxaemia. All alcohol drinking groups had enrichment for circulating Fusobacteria
Alcoholic hepatitis (cont.)		
Ciocan et al. 2018 (REF.[72])	• Analysis of gut microbiota composition and faecal and plasma bile acids • Patients without cirrhosis or alcoholic hepatitis ($n = 61$) • Patients without cirrhosis with alcoholic hepatitis ($n = 13$) • Patients with cirrhosis without alcoholic hepatitis ($n = 17$) • Patients with cirrhosis with alcoholic hepatitis ($n = 17$)	Patients with cirrhosis and alcoholic hepatitis had higher total plasma bile acid levels, whereas faecal levels of total and secondary bile acids were lower than other groups. These patients had higher relative abundance of Actinobacteria and lower relative abundance of Bacteroidetes

Nat Rev Gastrenterol Hepatol 2019 Apr, 16(4),235-246

Probiotic function in Alcohol-Associated Liver Disease

Table 2: Probiotics in ALD—clinical evidence.

Disease	Treatment and duration	Observations
Alcoholic cirrhosis patients, $n = 10$	VSL#3 treatment for 3 months	Reduced plasma ALT, AST, and GGT levels; normalized plasma TNF-α, IL-6, and IL-10 levels; and decreased MDA, 4-HNE, and S-NO levels
Alcoholic cirrhosis patients, $n = 20$	*Lactobacillus casei* Shirota for 4 weeks of treatment	Normalized phagocytic capacity, decreased TLR4, sTNFR1, sTNFR2, and IL10 levels
Alcoholic cirrhosis patients, $n = 34$	*Escherichia coli* Nissle for 42 days of treatment	Improvement in intestinal colonization, restored microflora in feces, and reduced endotoxin levels in blood
Alcoholic cirrhosis patients, $n = 12$	A mixture of different lactic acid bacteria strains treated for 2 months	Positive effects on ecological balance of enteric commensals, reduced ALT, γ-GT, and TNF-α levels
Patients with alcoholic psychosis and liver disease, $n = 66$	*Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 for 5 days of treatment	Increased numbers of both *Bifidobacteria* and *Lactobacilli*; reduction in ALT, AST, GGT, LDH, and total bilirubin
Alcoholic and nonalcoholic cirrhosis and hepatic encephalopathy patients $n = 89$	VSL#3 treatment for 6 months	Reduced risk of hospitalization for HE (hepatic encephalopathy), improved CTP (Child-Turcotte-Pugh) and MELD (model for end-stage liver disease) scores

.Gastrenterol Res Pract 2016;2016:5491465

Probiotics and Alcohol-Associated Liver Disease……

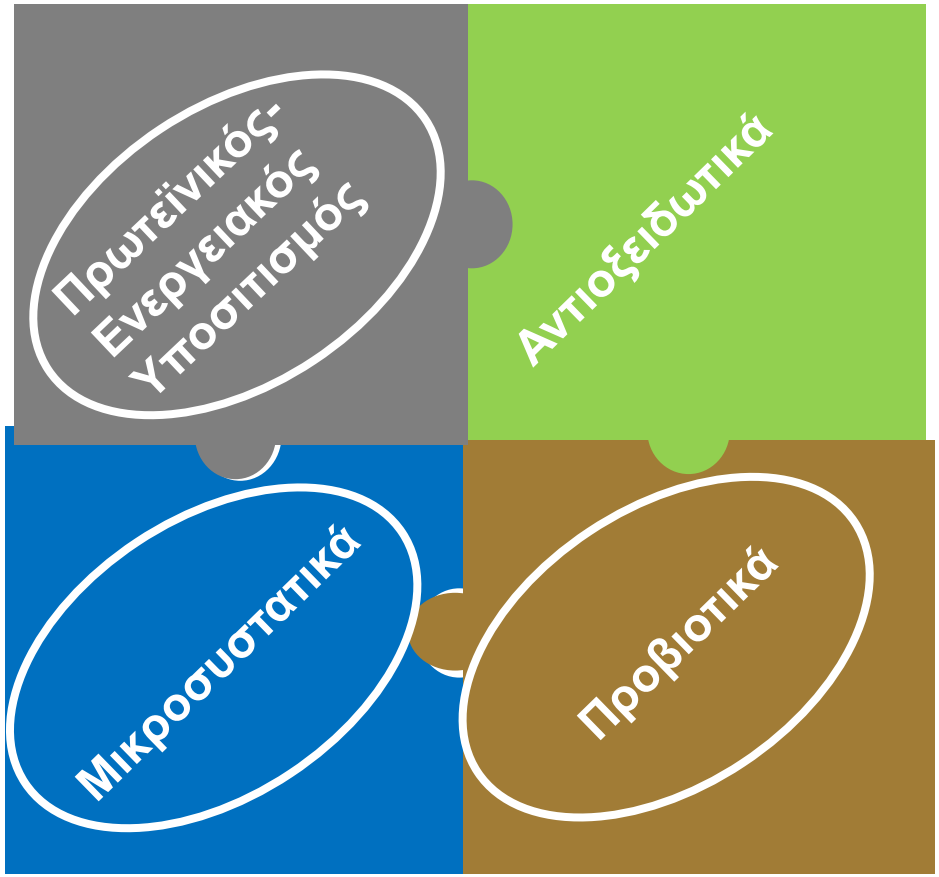
Probiotics for people with hepatic encephalopathy

Compared with placebo or no intervention, probiotics improve recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations, but probiotics may lead to little or no difference in mortality Cochrane Systematic Review, 23, 2017

Effect of probiotics and synbiotics consumption on serum concentrations of liver function test enzymes: a systematic review and meta-analysis

Probiotics and synbiotics may be suggested as supplements to improve serum concentration of liver enzymes, especially when synbiotics administered for a period ≥ 8 weeks and in individuals with liver disease European journal of Nutrition **2018,**57, 2037–2053

Διατροφικές Προκλήσεις στην Ηπατοπάθεια σχετιζόμενη με το Αλκοόλ



Nutritional Deficiencies

Table 4
Prevalence, testing, and treatment for specific deficiencies

	Prevalence	Testing	Treatment
Calories		Evaluate in all patients with ALD	35–40 kcal/g/kg BW/d in patients with liver cirrhosis
Protein		Evaluate in all patients with ALD	1.2–1.5 g/kg BW/d in patients with liver cirrhosis
Vitamin A	Prevalence data limited	Test in patients with findings suggestive of deficiency	Treat on a case-by-case basis; use caution in patients who continue to ingest alcohol, which can potentiate hepatotoxicity
Vitamin B_{12}	25% of hospitalized patients with chronic alcohol consumption	Test in patients with findings suggestive of deficiency	Replete and monitor B_{12} levels if deficiency exists
Folate	80% of hospitalized patients with chronic alcohol consumption	Test in patients with findings suggestive of deficiency	Replete and monitor folate levels if deficiency exists
Vitamin D	86.5% of patients with cirrhosis, 49.0% in patients with liver disease without cirrhosis	High prevalence in chronic liver disease (86.3%); although limited data exists, can consider screening	Single large dose of ergocalciferol compared with cholecalciferol may be more effective in alcoholic liver disease
Vitamin E	Prevalence data are limited	Test in patients with findings suggestive of deficiency	Treat if deficiency exists; no proven benefit of supplementation in absence of deficiency
Zinc	83% of patients with cirrhosis	Test in patients with findings suggestive of deficiency	Zinc supplementation improved Child-Pugh class at 3 mo in alcoholic cirrhosis; further studies are needed but, one can consider supplementation

Clin Liver Dis 23 (2019) 99–114

Vitamin D deficiency in patients with liver cirrhosis

Author [ref]	Year (publication)	Etiology of liver disease	Study population (n)	Proportion of cirrhotics/ALF patients included	Study in favor of hypovitaminosis	Vitamin D levels
Terrier *et al* [67]	2011	HIV-HCV	189	25% F3-F4 0% F0	Yes	F3/F4: 16.2±10.0 ng/mL; F2: 18.9±8.5 ng/mL; F1: 20.9±11.1 ng/mL
Putz-Bankuti *et al* [68]	2011	Various, mainly alcohol (61%)	75	100% cirrhotic (33 CP-A, 32 CP-B, 10 CP-C)	Yes	Baseline: 16.0±9.2 ng/mL
Bitetto *et al* [69]	2011	HCV	211	Decompensated disease excluded, baseline staging: 2 (0-6 Ishak stage)	Yes	Median: 20.7 ng/mL (2.1-59.6); 46.4% <20 ng/mL; 16.1% <10 ng/mL
El-Maouche *et al* [70]	2013	HIV-HCV	116 African-American	13 cirrhotics	Yes	41% <15 ng/mL
Venu *et al* [71]	2013	Various, mainly alcohol and HCV	63	Liver transplant candidates	Yes	75% <20 ng/mL; 6.3% <10 ng/mL
Stokes *et al* [72]	2014	Various, mainly alcohol (66%)	65	100% cirrhosis, 82% with advanced disease (CP: B,C stage)	Yes	Median: 8.2 ng/mL (4.0–95.8)
Anty *et al* [73]	2014	Various, mainly alcohol (71%)	88	100% cirrhosis, with active infection	Yes	Median: 8.8 (5.3–14.1) ng/mL
Savic *et al* [74]	2014	Alcohol	30	100% cirrhosis	Yes	66.7% <50 ng/mL
Finkelmeier *et al* [75]	2014	Various, mainly alcohol and HCV	200	HCC	Yes	Mean: 17±13 ng/mL (1–72)
Kitson *et al* [77]	2013	HCV genotype 1	274	15% cirrhotics with compensated disease	No	Mean: 79.6 nmol/L; 48% <75 nmol/L; 16% <50 nmol/L

ALF, advanced liver fibrosis; CP, Child-Pugh stage; HCC, hepatocellular carcinoma

Ann Gastroenterol 2016, 29 (3), 297-306

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin D supplementation for chronic liver diseases in adults (Review)

- 15 randomized clinical trials
- 1034 participants
- 6 trials had baseline 25-hydroxyvitamin D levels (20 ng/mL),
- 9 trials were vitamin D insufficient (less than 20 ng/mL).
- Vitamin D orally
- Mean duration of vitamin D supplementation was 0.5 years and follow-up was 0.6 year

Η επίδραση της βιταμίνης D στη θνησιμότητα από οποιαδήποτε αιτία και στη θνησιμότητα λόγω ηπατικής ανεπάρκειας δεν ήταν στατιστικά σημαντική και απαιτούνται περισσότερες μελέτες

Zinc supplementation and Hepatic Encephalopathy

Zinc supplementation was associated with:

- Reduced progression to HCC (p = 0.0362)
- Improvement in the Child–Pugh score (p = 0.001)
- Improvement in bilirubin levels (p ≤ 0.005)
- Lower incidence of ascites (p = 0.08)
- Decrease in ammonia levels (p = 0.0114)

Η συμπληρωματική χορήγηση του Zn έχει στατιστικά σημαντική διαφορά συγκριτικά με placebo στη βελτίωση της εγκεφαλοπάθειας

Zn supplementation vs. placebo. Outcome; hepatic encephalopathy

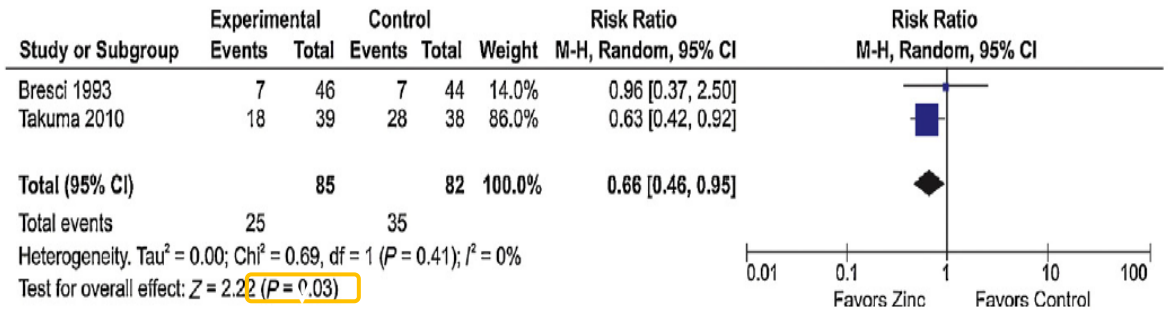
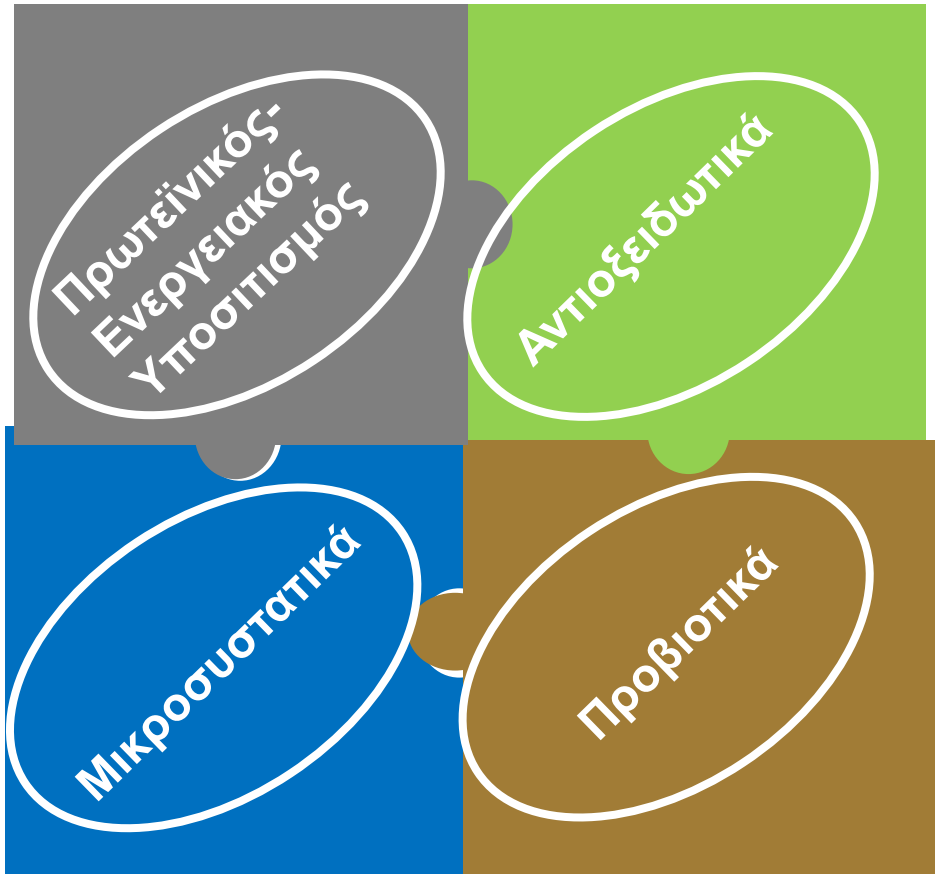


Fig. 3. Meta-analysis of the 'improvement of hepatic encephalopathy' outcome in studies comparing zinc supplementation vs placebo for the treatment of hepatic encephalopathy.

Διατροφικές Προκλήσεις στην Ηπατοπάθεια σχετιζόμενη με το Αλκοόλ



Vitamins and Minerals in Alcohol-Associated Liver Disease

Vitamin A

Μελέτες in vitro και in vivo υποστηρίζουν ότι η βιταμίνη Α έχει αντιφλεγμονώδη δράση στην αλκοολική ηπατοπάθεια. Απαιτούνται περισσότερες μελέτες για να αποδείξουν τη θεραπευτική της δράση *(Liver Int. 2014: 34: 343–352)*

Vitamin E

- 25 ασθενείς με αλκοολική ηπατίτιδα έλαβαν 1000IU E για 3 μήνες
- 24 μάρτυρες ελέγχου έλαβαν placebo
- Δεν υπήρχε διαφορά στα επίπεδα των ηπατικών ενζύμων J Hepatol 2004 Jan;40(1):40-6.

Vitamin C

Μελέτες in vivo δείχνουν προστατευτική δράση έναντι της αλκοολικής ηπατοπάθειας

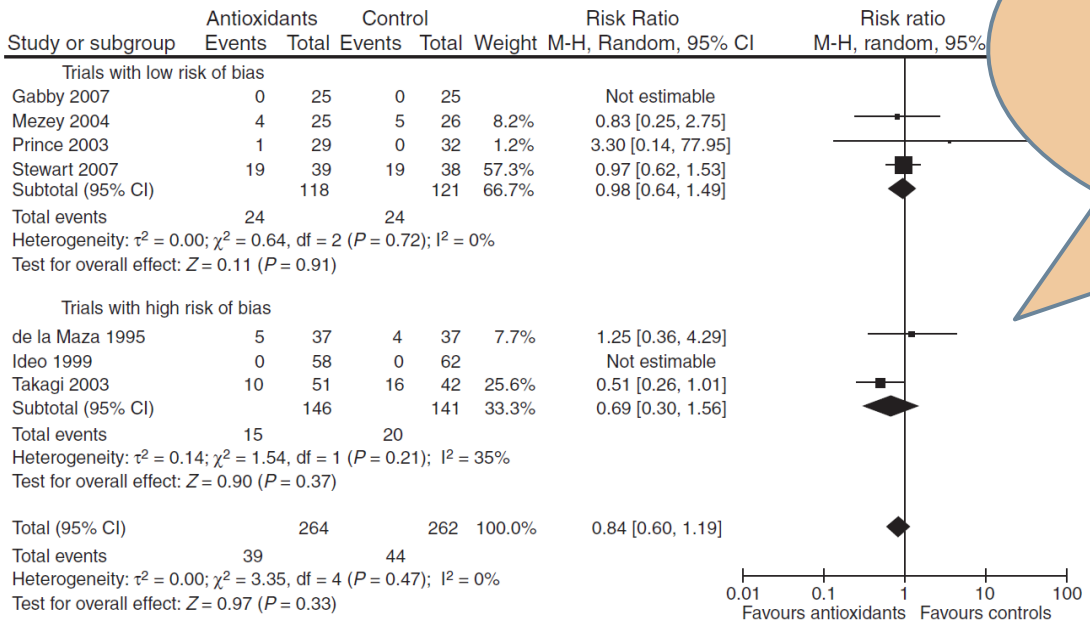
Magnesium

- 59 ασθενείς με αλκοολική ηπατοπάθεια χορηγήθηκε Mg ενδοφλεβίως και από το στόμα (12.5 mmol ημερησίως ή placebo για 6 εβδομάδες)
- Δεν υπήρχε διαφορά στη μυική μάζα και δύναμη *Scandinavian Journal of Gastroenterology, 2005; 40: 972/979*

Digestive and Liver Disease 47 (2015) 819–825

Antioxidant supplements for liver diseases

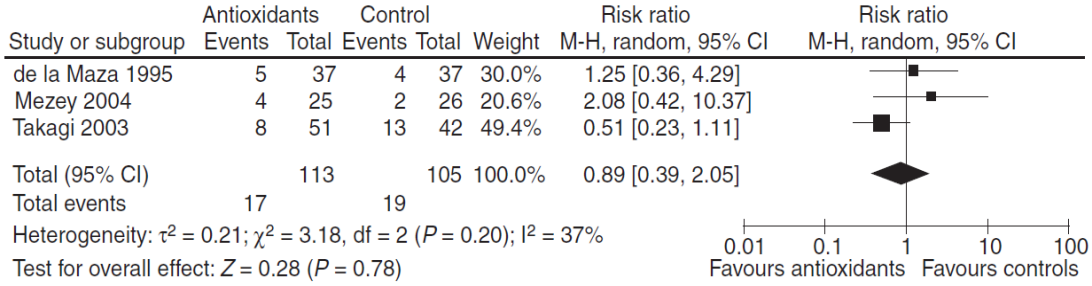
All-cause Mortality



Δεν υπάρχουν στατιστικά σημαντικές διαφορές στη χρήση αντιοξειδωτικών για τη θνησιμότητα οποιασδήποτε αιτιολογίας και για τη θνησιμότητα λόγω ηπατικής ανεπάρκειας

- 20 μελέτες
- 1225 ασθενείς
- .Περιλαμβάνουν beta-carotene (3 μελέτες), vitamin A (2 μελέτες), vitamin C (9 μελέτες), vitamin E (15 μελέτες) and selenium (8 μελέτες)

Liver-Related Mortality



Stratification according to the type of liver disease assessed did not affect the conclusions

Aliment Pharmacol Ther 2010; 32: 356–367

S-adenosylmethionine (SAMe) in Alcohol-Associated Liver disease

Study, [Ref.]	Design	Subjects (n)	SAMe dose (g/d)	Duration	Outcomes
*Altomare *et al.*, 1988 [120]	RCT	18 inpatients with severe decompensated ALD; 17 outpatients with ALD	1.2 g/d po *vs.* placebo	4 wk or 6 mo	Significantly increased hepatic glutathione, cysteine, taurine and reduced methionine
*†Chawla *et al.*, 1999 [121]	RCT	7 patients with stable ALD cirrhosis	800 mg/d iv *vs.* placebo	17 d	Improved clinical biochemistry and hepatic methionine handling
*Cibin *et al.*, 1988 [122]	RCT	64 patients with alcohol dependence but not cirrhosis	200 mg/d im *vs.* placebo	30 d	Reduced anxiety, depression, gGT and alcohol consumption
*†Corrales *et al.*, 1991 [123]	RCT	16 patients with ALD	1.2 g/d po *vs.* placebo	4 wk	Improved hepatic methionine handling
*Diaz Belmont *et al.*, 1996 [124]	RCT	45 alcoholic hepatitis patients	200 mg/d iv *vs.* placebo	15 d	Increased plasma glutathione
*Loguercio *et al.*, 1994 [125]	RCT	40 (20 non-cirrhotic, 20 cirrhotic)	2 g/d iv *vs.* placebo	15 d	Increased RBC glutathione and cysteine concentrations
*Mato *et al.*, 1999 [85]	RCT	123 patients with ALD cirrhosis	1.2 g/d po *vs.* placebo	24 mo	SAMe improved survival and reduced liver transplantation in Child-Pugh A/B patients
*†Trespi *et al.*, 1997 [126]	RCT	210 patients with ALD	SAMe 1.5 g/d plus ursodeoxycholic/tauroursodeoxycholic acid *vs.* ursodeoxycholic/tauroursodeoxycholic alone	24 wk	Greatest clinical biochemistry improvement with SAMe plus tauroursodeoxycholic acid
*Vendemiale *et al.*, 1989 [46]	RCT	39 patients with ALD	No treatment *vs.* SAMe 1.2 g/day *vs.* placebo	24 wk	SAMe significantly increases total glutathione
Medici *et al.*, 2011 [87]	RCT	37 (14 with biopsies pre and post-treatment)	1.2 g/d *vs.* placebo	24 wk	No improvement in clinical, biochemical or histological disease
#Fiorelli *et al.*,1999 [66]	NR, open label	640 IHC patients (18% ALD)	800 mg/d iv or 500 mg/d im	15 d	Clinical biochemistry and symptomatic improvement

Journal of Hepatology 2012 , 57 , 1097–1109

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S-adenosyl-L-methionine for alcoholic liver diseases

- 9 randomized clinical trials
- 434 participants with alcoholic liver disease

Δεν υπήρχε στατιστικά σημαντική διαφορά στη θνησιμότητα από οποιαδήποτε αιτία και στη θνησιμότητα λόγω ηπατικής ανεπάρκειας ή στις επιπλοκές με τη χορήγηση SAMe και απαιτούνται περισσότερες μελέτες

One clinical trial showed to lower level of liver enzymes with 200 mg of glycyrrhizin for 5d per week for approximately 10 years in hepatitis C *Patients Cancer 1997*

Low dosage of curcumin prevented HS compared with the alcohol control group *Life Sci 2013*

Table 2 The information of effects of current natural medicines on the treatment of alcoholic liver disease

Medicine/ compound	Type of model	Dosage/duration	Effects	Mechanisms
Vitamin E and C	Malnourished rats with ethanol	Vitamin E (15 mg/kg) Vitamin C (10 mg/kg); single and combined treatments	Decreased ethanol induced hepatic glutathione peroxidase activity and hepatic fibrosis; Attenuated the development of hepatomegaly and hepatic necroinflammation	
Epigallocatechin-3-gallate (EGCG)	Male albino Wistar rats with Ethanol (6 g/kg per day) for 60 d	EGCG (100 mg/kg per day) for the last of 30 d of ethanol administration	Normalization of activities of enzymatic antioxidants; Reduction of lipid peroxidation	
	Female Sprague-Dawley rats with ethanol (56%)	EGCG (100 mg/bw)	Partly blocked the gut leakiness; Reduced endotoxemia and lipid peroxidation	Blunted the elevated expressions of CD14, TNF-α, COX-2 and iNOS
	Male Wistar rats with ethanol for 5 wk	EGCG contained diet (3 g/L) for 2 wk and then ethanol-EGCG diet for 5 wk	Reduced serum AST and ALT	Enhancement of FA oxidation through increasing of CTP-1 and p-ACC expression
Silymarin (*Silybum marianum*)	RCT, double-blind, 170 patients with cirrhosis	140 mg/d for 3 times orally	Reduced the rate of mortality No side effect	
	Alcohol induced baboons (50% of calories)	0.84 mg/calorie for 36 mo	Improve histologic stage of fibrosis	Decrease collagen I and (I) procollagen
	Alcohol and high fat induced rats	100 mg/kg per day, 150 mg/kg per day, 200 mg/kg per day for 6 wk	200 mg/kg per day decrease serum ALT and AST and hepatic fat contents	Attenuated NF-κB p65, ICAM-1 and IL-6 were found in silymarin groups (150 mg/kg, 200 mg)
Betaine	Ethanol diet Wistar rats	1% (w/v) in diet	Decrease hepatic ballooning and fat contents	Attenuate NOS production; Decrease CYP2E1 protein and activity
	High fat containing ethanol diet rats 6 g/kg for 8 more wk	200 and 400 mg/kg per day for 4 wk	Decrease ALT and AST	Inhibition of TLR-4 expression; Decrease serum endotoxin, TNF-α, IFN-γ and IL-18
Glycyrrhizin (*Glycyrrhiza glabra*)	Ethanol-CCl_4 induced male SD rats	Intraperitoneal injections of potenlin (acquired from Hai Ning Pharmaceutical Co., Zhe Jiang, China)	Decreasing serum ALT levels	Normalized NF-κB binding activity
Ginsenosides	Ethanol-feeding mice Ethanol feeding hepatocytes (AML12 cell lines)	Red ginseng extract containing abundant ginsenosides (Rb1, Rb2, and Rd) (250 mg/kg or 500 mg/kg) for 4 wk in mice	Improves chronic alcohol-induced histopathological changes; Decreases in hepatic triglyceride content	Inhibition of lipogenesis pathway; Attenuated EtOH-induced cytochrome; P450 2E1, 4-hydroxynonenal, and nitrotyrosine levels; Activation of AMPK-SIRT1
Fenugreek seed polyphenol	Alcohol consumption with high fat diet mice	Red ginseng (200 mg/kg per day) for last 2 wk	Lower ALT levels and no different AST	Reduced level of TNF-α and IL-1 and increase IL-10
	EtOH (30 mM) induced Chang liver cells	20, 40, 60 mg/mL	Increased GSH/GSSG ratio Reduced EtOH-induced LDH leakage	Inhibition of NF-κB
	Ethanol induced rats (6 g/kg per day) for 30 d	200 mg/kg per day for 30 d	Improved lipid profile and reduced collagen content, crosslinking, aldehyde content and peroxidation	
Curcumin	Alcohol (100 mM) induced rat primary hepatocytes	0-50 μmol/L	Ameliorated MDA and AST	Improved GSH and heme oxygenase-1 (HO-1) induction
	Alcohol-induced female Sprague-Dawley rats	400 mg/kg bw	Improved liver pathology, decreasing elevation of hepatic MDA	Suppressing of NF-κB activation
LIV-52	Ethanol-induced HepG2 cells (100 and 200 mM)	1% or 2% Liv.52 for 24 h		Normalized suppressed PPAR-α and induced TNF-α

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Cochrane Library

Cochrane Database of Systematic Reviews

Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases (Review)

- 13 randomized clinical trials
- 915 patients with alcoholic and/or hepatitis B or C virus liver diseases

Το γαϊδουράγκαθο έναντι placebo δεν είχε στατιστικά σημαντική διαφορά στη θνησιμότητα, στις επιπλοκές και στην ιστολογική εικόνα του ήπατος.
Δεν προκαλεί παρενέργειες

On going Clinical Trials in Alcohol-Associated Liver Diseases

NCT Number	Title
NCT03938662	S-adenosylmethionine Plus Choline in Treatment of Patients With Alcoholic Liver Disease
NCT01501162	Effect of Probiotics on Gut-Liver Axis of Alcoholic Liver Disease
NCT03503708	Herbal Supplements for Improvement of Liver Function in Participants With Alcoholic Liver Disease
NCT02335632	Effect of Probiotics on Gut-Liver Axis of Alcoholic Hepatitis
NCT00573313	Effects of SAMe in Patients With Alcoholic Liver Disease
NCT00851981	Randomized, Controlled Trial of S-adenosylmethionine in Alcoholic Liver Disease
NCT00863785	Treatment of Severe Alcoholic Hepatitis With Corticoids Plus N Acetyl Cysteine Versus Corticoids Alone
NCT00200746	Treatment of Alcohol-Related Hepatitis With Arginine
NCT03732586	Effect of Omega 5 Fatty Acid as an Adyuvant Treatment to Prednisone in Patients With Severe Alcoholic Hepatitis
NCT04084522	Effect of Saturated Fat (Desi Ghee) on Gut-Liver Axis in Alcoholic Hepatitis
NCT04250259	SAMe Trial for Patients With Alcoholic Cirrhosis
NCT02072746	Zinc Supplementation in Alcoholic Cirrhosis

Διατροφικές Προκλήσεις στην Ηπατοπάθεια σχετιζόμενη με το αλκοόλ

- Κάλυψη ενεργειακών και πρωτεϊνικών αναγκών 30-35kcal/kg, 1.2-1.5g/kg/d

  - Αναλυτικό διατροφικό ιστορικό
  - Αποφυγή περιοριστικών διαιτών
  - Ενεργειακά πυκνά γεύματα
  - Γευματίδια προ ύπνου για να αποφεύγονται τα μεγάλα διαστήματα νηστείας
  - Επανέλεγχος

- Η εντερική σίτιση και η παρεντερική σίτιση θα πρέπει να δίνεται όταν κρίνεται απαραίτητη
- Συμπληρώματα με BCAA θα μπορούσαν να δοθούν στην ηπατοπάθεια σχετιζόμενη με αλκοόλ
- Τα προβιοτικά θα μπορούσαν να χρησιμοποιηθούν
- Οι ελλείψεις σε μικροσυστατικά θα πρέπει να καλύπτονται
- Τα αντιοξειδωτικά δεν φαίνεται να έχουν αποτέλεσμα
- Άσκηση

- Αποχή από το αλκοόλ

Guidelines in Alcohol-Associated Liver Disease

ACG 2018

Protein:1.2 to 1.5 g/kg, Energy:35 Kcal/kg.
Zinc Thiamine and B complex vitamins need to be replaced.
Antioxidant cocktails and vitamin E have not shown beneficial effects

AASLD 2020

Enteral nutritional supplements
zinc should be considered in moderate and severe AH.

EASL 2018

Protein:1.2 to 1.5 g/kg, Energy:35 Kcal/kg
Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended.

ESPEN 2019

Protein:1.2 to 1.5 g/kg, Energy:35 Kcal/kg
B vitamins, zinc and vitamin D, replacement of these may be beneficial

ALEH-GLEHA 2019

Protein 1.2–1.5 g/kg Energy 30-35 kcal/kg,
late-evening snack.
Vitamins (i.e.thiamine, folate, pyridoxine and cyanocobalamin) and minerals (i.e.potassium, phosphate, magnesium and zinc) should be measured and/or supplemented as needed

KASL 2018

CHO: 2-3 g/kg/day, Protein:1.2 to 1.5 g/kg, Energy:35 Kcal/kg
In the presence of hepatic encephalopathy, administration of a branched-chain amino acid (BCAA)
smaller and frequent meals A late-evening snack of 200 kcal
adequate amounts of vitamin A, thiamine,vitamin B12, folic acid, pyridoxine, vitamin D, and zinc can be considered Less than 5 g/day of salt intake (sodium: 2 g/day, 88 mmol/day) is recommended.

Σας Ευχαριστώ!

Τμήμα Διατροφής
ΓΝΑ Ευαγγελισμός