جمعية الطب الداخلي الجامعي لولاية تلمسان

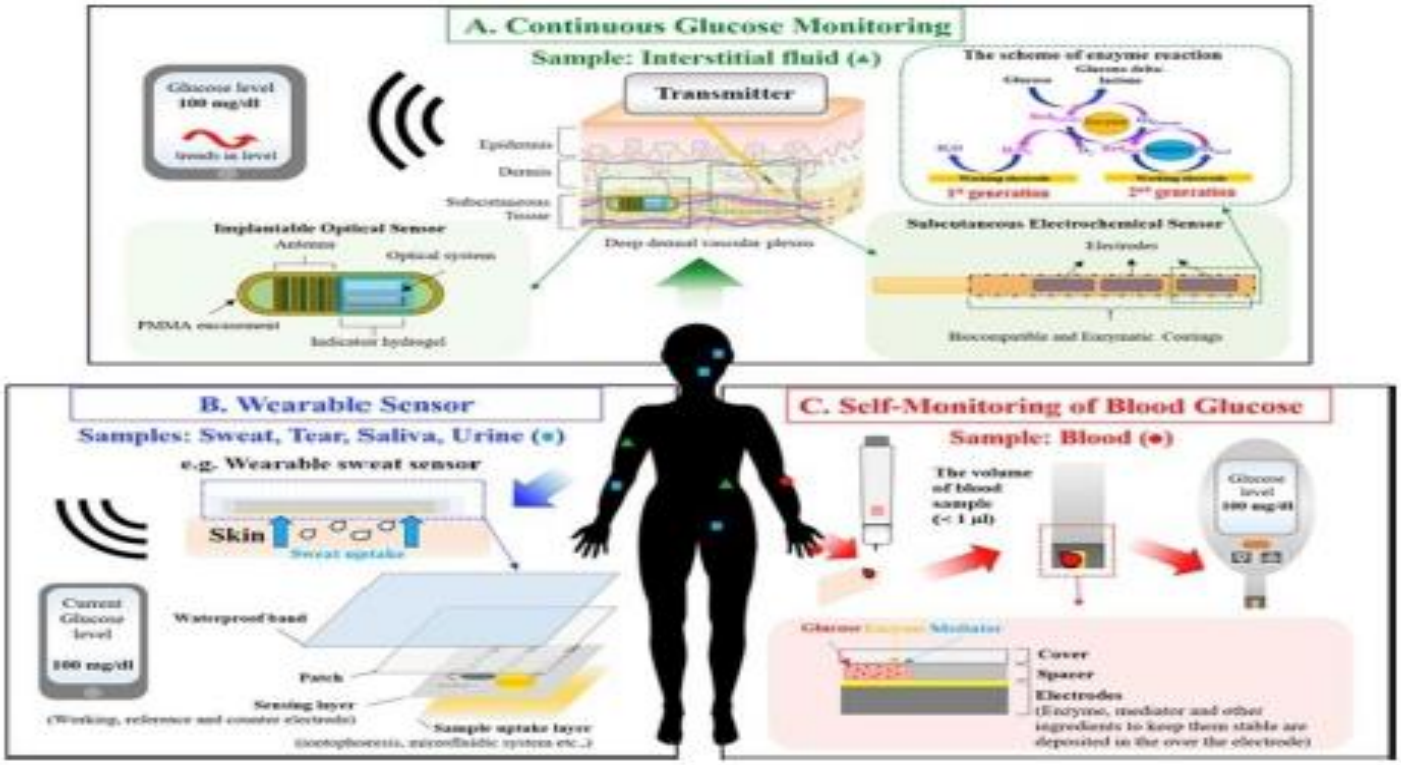
5th SÉMINARY OF LAREDIAB

11TH CONGRESS OF AMIWIT

Friday 9 & Saturday 10 December 2022

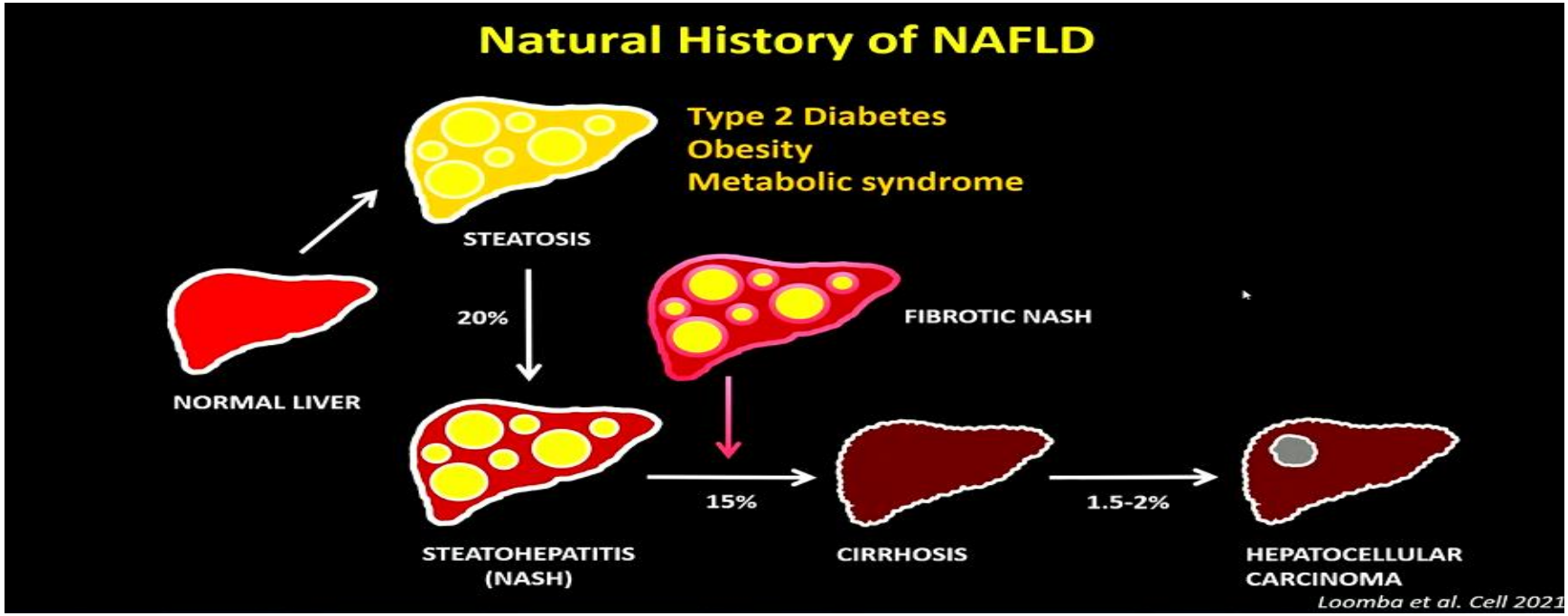
الجمعة 15 و السبت 16 جمادى الأولى 1444

FACULTY OF SNV/STU - UNIVERSITY OF TLEMCEN



Liver fibrosis

NASH fibrotic

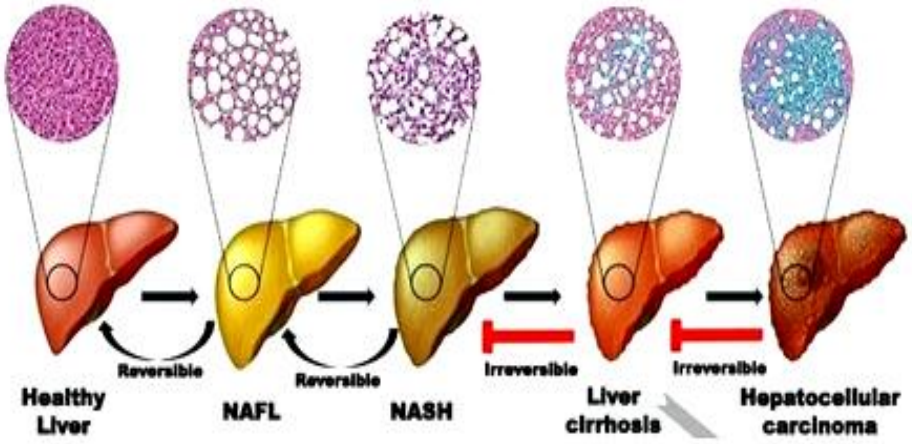


Dr. BouabdAllah Kahouadji Nesrine
Assistant Master in Internal Medicine/CHU Tlemcen

December 09, 2022

Introduction

- Diabetes Mellitus (DM) associated conditions
- Non-alcoholic fatty liver disease (NAFLD)
  - 25% non-DM, 50% DM1, 60-70% DM2
- DM aggravates progression
- Simple steatosis (>5%)
  - Regarded as benign
  - Increased risk with mild inflammation



Wang, J., He, W., Tsai, P. J., Chen, P. H., Ye, M., Guo, J., & Su, Z. (2020). Mutual interaction between endoplasmic reticulum and mitochondria in nonalcoholic fatty liver disease. *Lipids in Health and Disease*, *19*(1), 1-19.

Introduction

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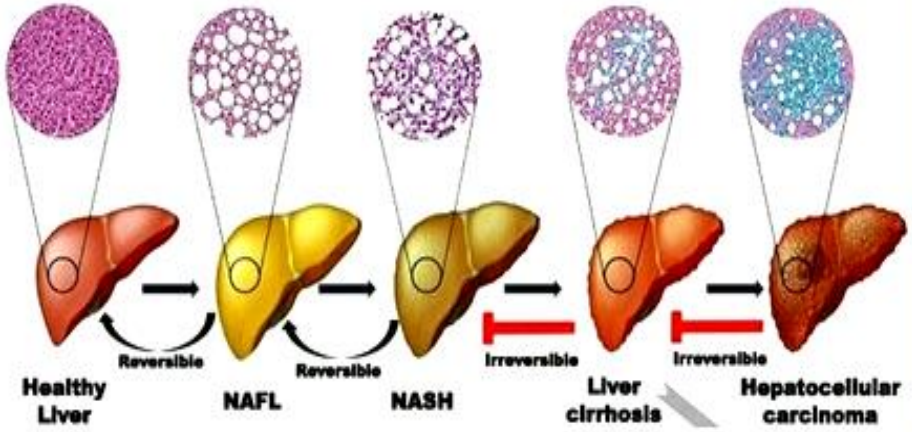


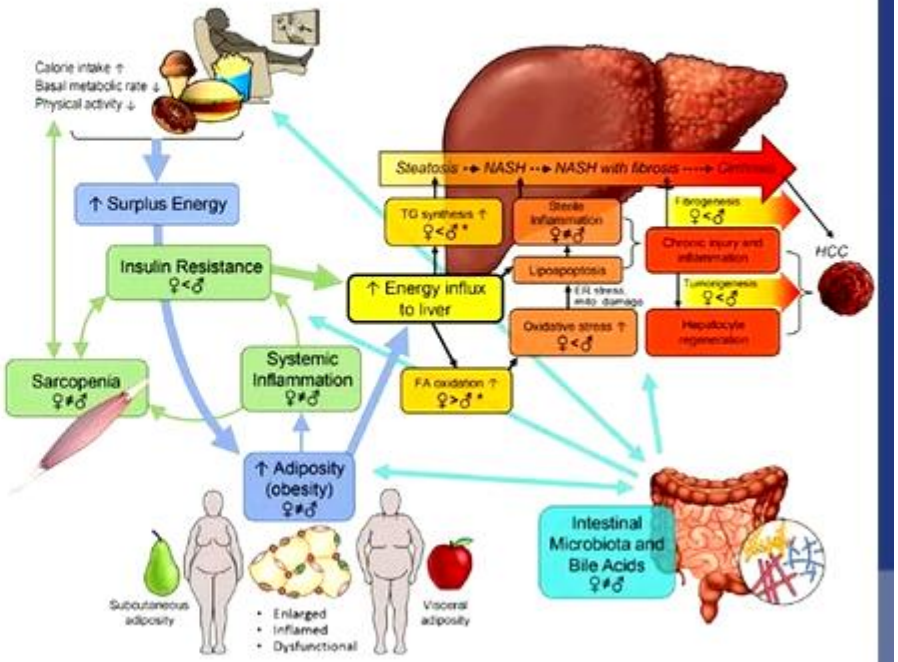
Determining the onset of steatosis may be relevant for early intervention

Wang, J., He, W., Tsai, P. J., Chen, P. H., Ye, M., Guo, J., & Su, Z. (2020). Mutual interaction between endoplasmic reticulum and mitochondria in nonalcoholic fatty liver disease. *Lipids in Health and Disease*, *19*(1), 1-19.

Introduction

- Sex and age differences

- NAFLD prevalence and severity
  - Non-DM men > women pre-menopause
  - Non-DM men < women post-menopause



What is the effect of sex/age/diabetes on hepatic fat and inflammation prior to NAFLD?

Amsterdam UMC
University Medical Centers

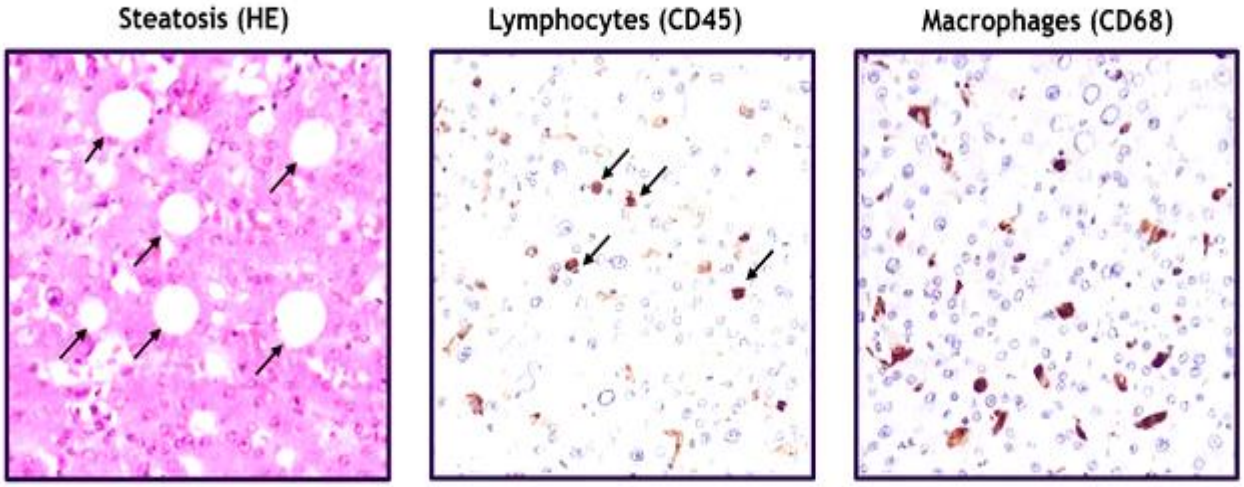
Hepatic fat and macrophages are increased in livers of diabetic patients without NAFLD

21 September 2022

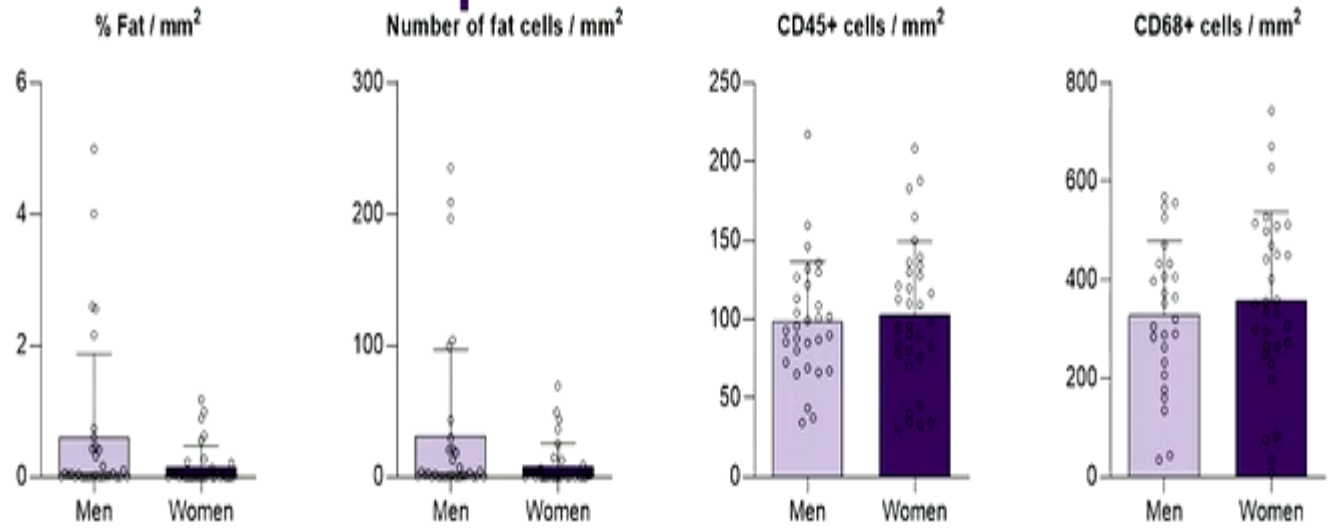
Amber Korn

Methods

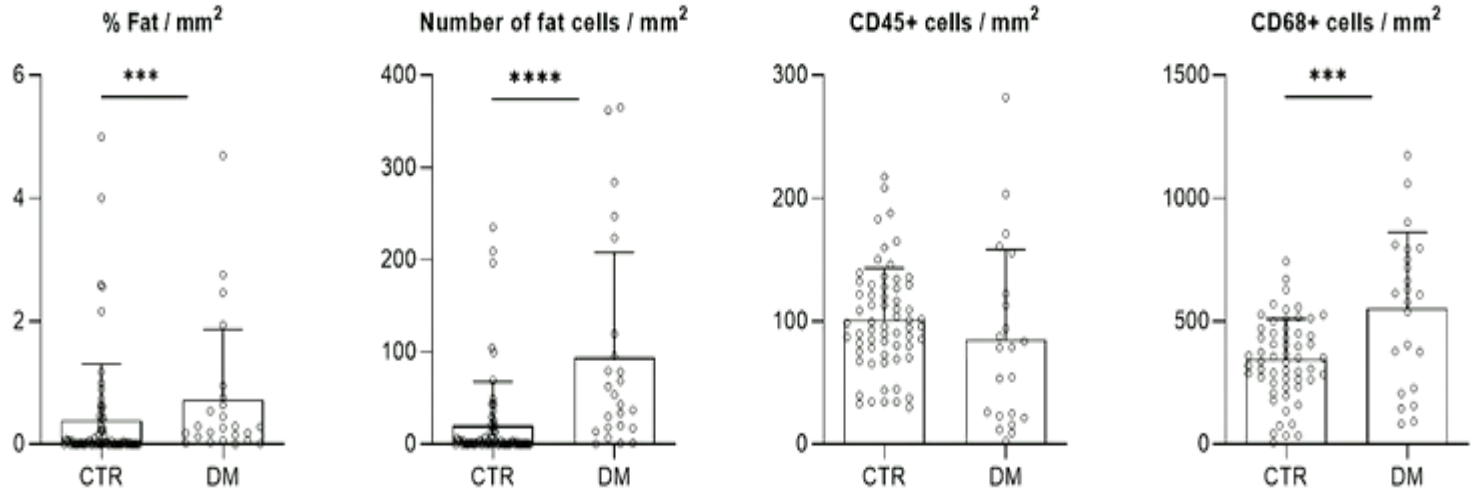
- 66 non-DM and 24 DM patients
  - Liver biopsy acquired at autopsy
  - No clinical or histopathological NAFLD (<5% steatosis)



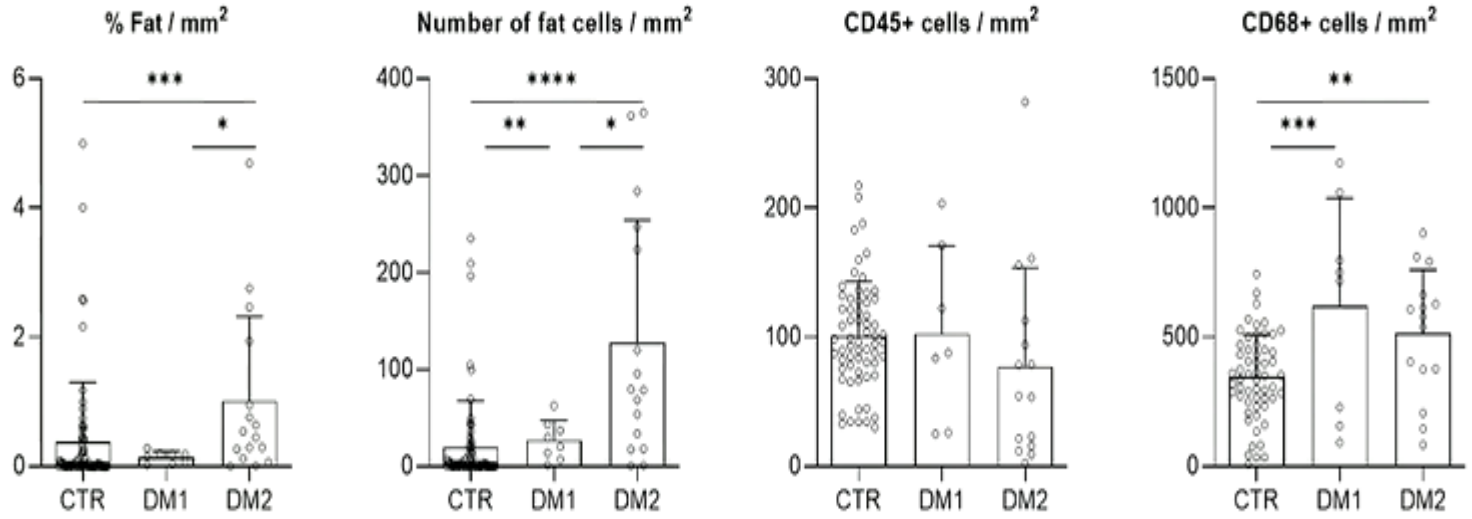
No effect of sex or age on hepatic fat and inflammation in patients without diabetes



Significantly more hepatic fat and macrophages in patients with diabetes



Significantly more hepatic fat in DM2, and macrophages in DM1 & DM2 patients



Discussion

- Increased hepatic fat in DM2 patients without NAFLD
  - Prone to develop NAFLD
  - Response to lifestyle?
- Increased macrophages in DM1/2 patients without NAFLD
  - Kupffer cells expansion
  - No association found between fat and inflammation
- No sex differences in patient group with or without DM
  - Metabolically distinct organs, reflected in NAFLD prevalence
  - Indications by comparing patient groups

Phthalate exposure is associated with NAFLD, but not liver fibrosis in the United States

Ciardullo S[1,2], Muraca E[1], Cannistraci R[1], Lattuada G[1], Perseghin G.[1,2]

[1]Medicine and Rehabilitation, Policlinico di Monza, Monza, Italy,
[2]Medicine and Surgery, University of Milano Bicocca, Milano, Italy.

Stefano Ciardullo

Phthalate exposure is associated with NAFLD, but not with liver fibrosis in the United States

Introduction

- Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting a quarter of the adult world population[1]
- NAFLD is strictly associated with metabolic dysfunction, including the metabolic syndrome, obesity, diabetes and hypertension[2]
- Apart from dietary and behavioral factors, recent evidence also suggests a potential contribution from environmental factors such as pollutants in its development and progression[3]

1 Younossi Z et al *Hepatology* 2016
2 Marchesini et al *Diabetes* 2001
3 Guo B et al *J Hepatol* 2022

Introduction

- Phthalates are a class of plasticizers widely used in industry and in a large range of daily life products including packaging materials for food, children and babies' toys, household items, paints, medical devices, as well as cosmetics and perfumes[1]
- Human beings are widely exposed to phthalates via dermal exposure, inhalation of polluted air and ingestion of contaminated food and water.

1 Carli F et al *Metabolites* 2022

Introduction

- Previous studies showed that these agents might act as endocrine disrupting chemicals, i.e., they may disrupt the metabolic and hormonal functions responsible for the maintenance of homeostasis, leading to obesity, type 2 diabetes and insulin resistance[1]

1 Lobstein T et al *Obes Rev* 2021

Aim

- To evaluate the association between urinary phthalate metabolites and both NAFLD and significant liver fibrosis in the general United States population.

Methods

Inclusion criteria

- Age ≥ 18 years
- Available Vibration controlled transient elastography (VCTE)
- Available Urinary phthalate metabolites

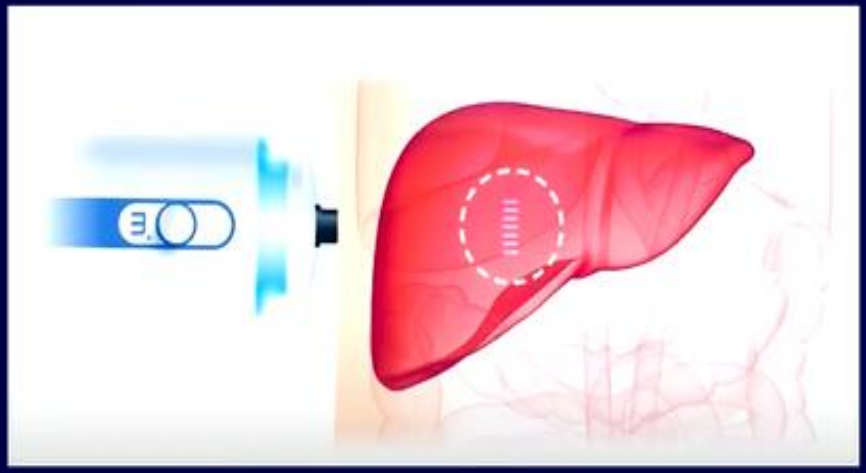
Exclusion criteria

- Viral hepatitis (HCV antibodies, HBsAg positive)
- Significant alcohol consumption (>30 g/d men, >20 g/day women)

Methods

VCTE

- Examinations were considered reliable only if at least 10 liver stiffness measurements (LSM) were obtained after a fasting time of at least 3 hours, with an interquartile range / median < 30%.
- CAP values ≥274 dB/m: steatosis[1]
- LSM values ≥8 kPa: significant fibrosis (≥F2)[2]

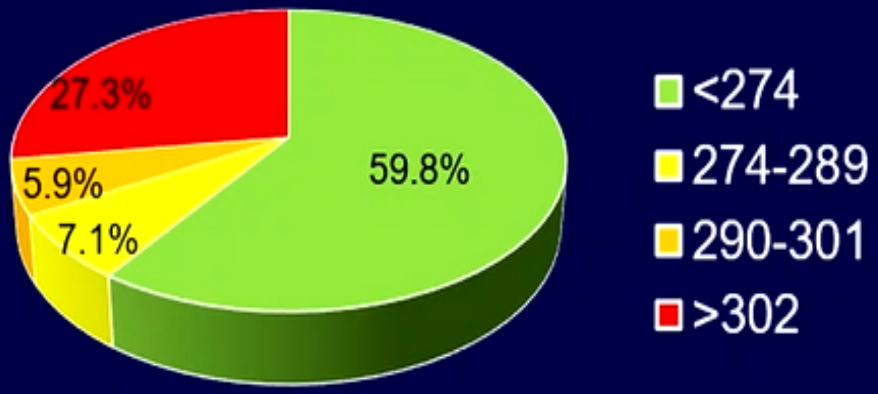


1 Eddowes P et al *Gastroenterology* 2019
2 Roulot D et al *J Hepatol* 2008

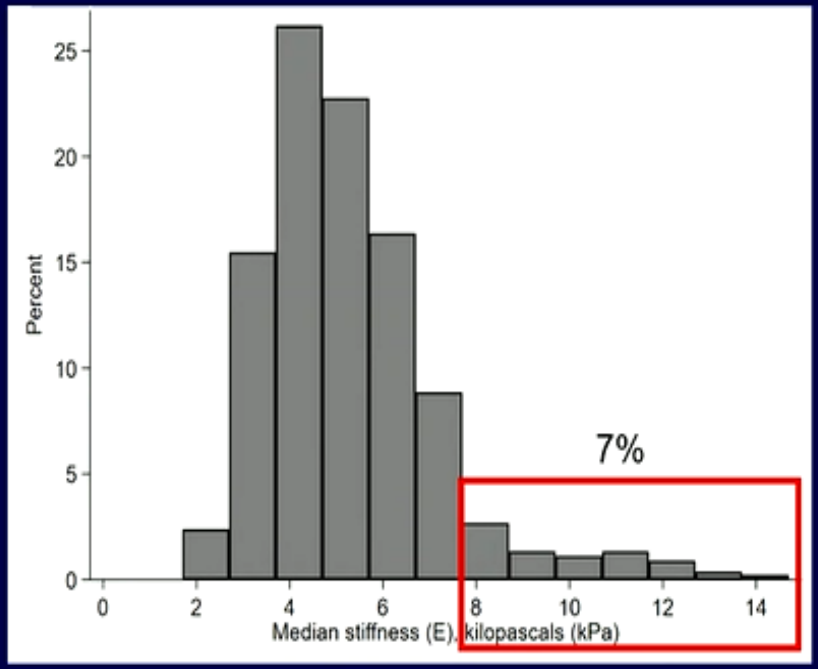
Results

1367 participants; mean age 46.4 yrs; 49.9% women; mean BMI 29.2 kg/m2; diabetes 12.5%

CAP values



LSM values



Results

	CAP (dB/m)				
	<274 (n=783)		>274 (n=584)		p-value
Age (years)	43.3	(0.9)	51.0	(0.9)	<0.01
BMI (Kg/m2)	26.3	(0.3)	33.6	(0.4)	<0.01
Female sex	416	(53.2)	263	(45.0)	<0.01
Waist Circumference (cm)	91.3	(0.7)	110.1	(0.9)	<0.01
Triglycerides (mg/dL)	115.5	(3.1)	186.7	(7.0)	<0.01
HDL-C (mg/dL)	56.5	(0.8)	47.8	(0.8)	<0.01
AST (IU/L)	21.3	(0.6)	22.0	(0.5)	0.444
ALT (IU/L)	20.2	(0.8)	26.4	(1.1)	<0.01
SBP (mmHg)	118.5	(0.7)	127.5	(0.9)	<0.01
DBP (mmHg)	71.5	(0.5)	75.2	(0.6)	<0.01
MEHHP (ng/mL)	6.4	(0.4)	8.0	(0.8)	0.034
MEHP (ng/mL)	1.5	(0.1)	1.6	(0.2)	0.749
MEOHP (ng/mL)	4.1	(0.2)	5.3	(0.6)	0.019
Diabetes	44	(5.8)	129	(22.3)	<0.01

Results

	LSM (kPa)				
	<8 (n=1256)		>8 (n=111)		p-value
Age (years)	46.0	(0.7)	52.4	(2.0)	0.023
Female sex	631	(50.2)	50	(44.9)	0.482
BMI (Kg/m2)	28.6	(0.3)	38.5	(1.0)	<0.01
Waist Circumference (cm)	97.2	(0.6)	121.4	(2.5)	<0.01
Triglycerides (mg/dL)	139.3	(3.5)	214.3	(19.4)	<0.01
HDL-C (mg/dL)	53.5	(0.6)	46.6	(2.0)	<0.01
AST (IU/L)	21.1	(0.4)	27.8	(2.3)	0.008
ALT (IU/L)	22.0	(0.6)	32.6	(2.9)	0.001
SBP (mmHg)	121.7	(0.6)	128.5	(1.8)	<0.01
DBP (mmHg)	73.1	(0.4)	72.2	(1.6)	0.645
MEHHP (ng/mL)	7.0	(0.4)	8.5	(1.8)	0.444
MEHP (ng/mL)	1.6	(0.1)	1.4	(0.2)	0.330
MEOHP (ng/mL)	4.5	(0.3)	5.4	(1.1)	0.426
Diabetes	123	(10.1)	49	(45.2)	<0.01

Conclusions

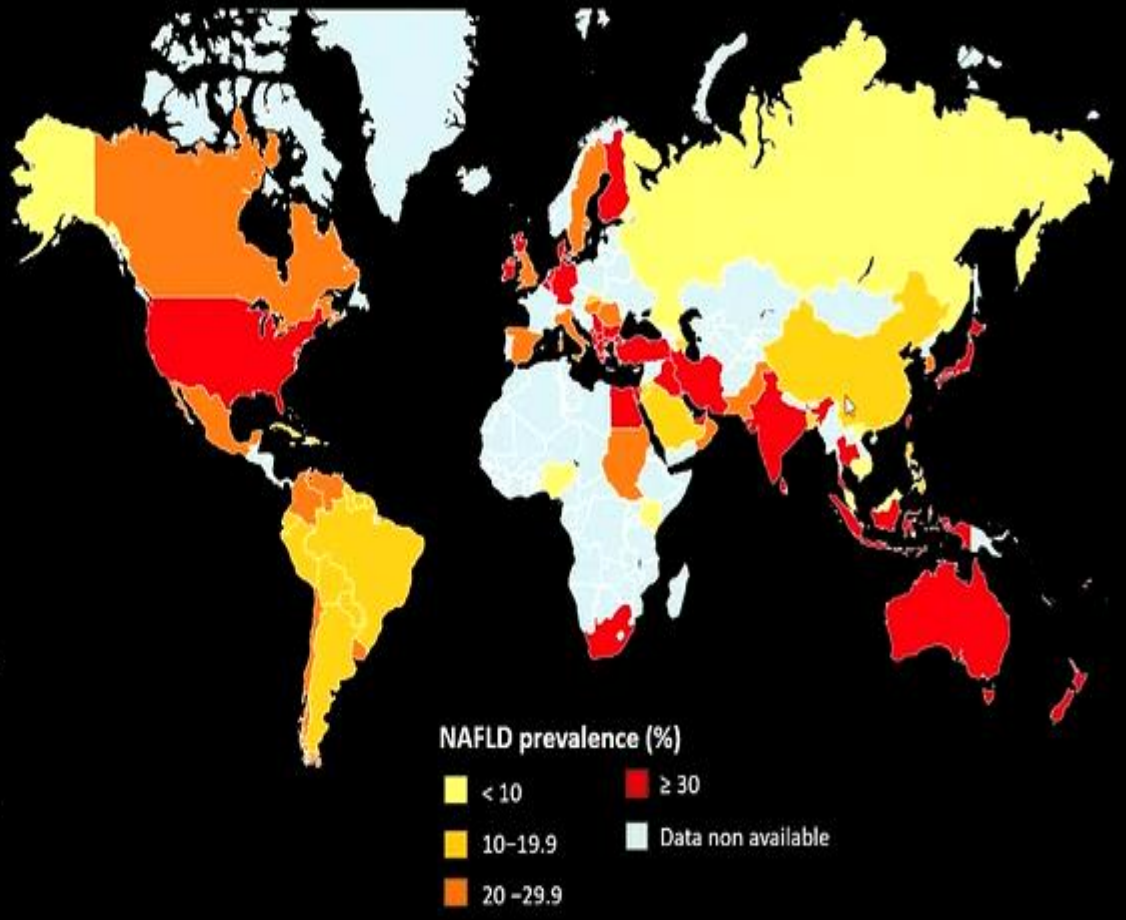
- NAFLD and to a lesser extent significant liver fibrosis are common in the general US population
- Obesity and diabetes are the major predictors of liver disease
- Higher urinary phthalate metabolites levels are associated with a higher prevalence of NAFLD, but not fibrosis, after adjustment for potential confounders

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD

1) Hepatic fat accumulation >5% according to histological analysis;
2) Insulin resistance;
3) Lack of excessive daily alcohol consumption or other secondary causes of hepatic disease.

Global prevalence 25%



Younossi et al. Nat Rev Gastroenterol Hepatol. 2018

UCBM
UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA

UNIVERSITY OF GOTHENBURG

The Fibrotic NASH Index: A Simple Non-Invasive Score to Screen for Liver Disease in Individuals With Metabolic Risk Factors

Federica Tavaglione[1,2], Oveis Jamialahmadi[2], Antonio De Vincentis[3], Sami Qadri[4], Vincenzo Bruni[5], Simone Carotti[6], Giuseppe Perrone[6], Dario Tuccinardi[7], Silvia Manfrini[7], Paolo Pozzilli[7], Antonio Picardi[1], Hannele Yki-Järvinen[4], Luca Valenti[8], Umberto Vespasiani-Gentilucci[1], Stefano Romeo[2,9]

[1]Clinical Medicine and Hepatology Unit, Campus Bio-Medico University, Rome, Italy; [2]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [3]Internal Medicine Unit, Campus Bio-Medico University, Rome, Italy; [4]Department of Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [5]Bariatric Surgery Unit, Campus Bio-Medico University, Rome, Italy; [6]Department of Pathology, Campus Bio-Medico University, Rome, Italy; [7]Department of Endocrinology and Diabetes, Campus Bio-Medico University, Rome, Italy; [8]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milano, Italy; [9]Clinical Nutrition Unit, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy.

September 21, 2022

Federica Tavaglione

The fibrotic NASH index: a simple non-invasive score to screen for liver disease in individuals with metabolic risk factors

Aim

To develop a simple non-invasive score based on routine laboratory tests to identify fibrotic NASH in individuals at high risk for NAFLD

External validation cohorts

Helsinki

Overweight/obesity
(n=370)

Inclusion:
Age 18-75 years

Exclusion:
Chronic viral hepatitis
Alcohol abuse
Other chronic liver diseases
Drugs

NAFLD assessed by liver biopsy

Liver Bible

Metabolic syndrome
(n=947)

Inclusion:
Age 18-65 years

Exclusion:
Chronic viral hepatitis
Alcohol abuse
Other chronic liver diseases
Drugs

NAFLD assessed by FibroScan® examination

UK Biobank

Overweight/obesity, type 2 diabetes
(n=5,368)

Inclusion:
Age ≥ 18 years

Exclusion:
Chronic viral hepatitis

NAFLD assessed by magnetic resonance imaging

Clinical characteristics of the study cohorts

	MAFALDA	Helsinki	Liver Bible	UK Biobank
n	264	370	947	5,368
Age, years	43.4 (10.1)	49.1 (9.5)	53.9 (6.3)	55.3 (7.3)
Women, n (%)	195 (74%)	262 (71%)	157 (17%)	2,406 (45%)
BMI, kg/m^2	41.6 (4.4)	42.3 (7.7)	28.5 (3.1)	28.8 (3.4)
Glucose, mg/dL	98 (92-106)	105 (96-114)	94 (87-103)	88 (83-95)
HbA1c, %	5.5 (5.3-5.9)	5.7 (5.4-6.2)	5.4 (5.2-5.6)	5.3 (5.1-5.6)
Cholesterol, mg/dL	179.1 (31.2)	163.8 (41.6)	202.1 (32.3)	224 (43)
HDL cholesterol, mg/dL	45.8 (9.8)	46.2 (12.1)	45.3 (10.1)	54 (12)
LDL cholesterol, mg/dL	121.3 (30.1)	99.1 (35.1)	123.3 (28.9)	143 (35)
Triglycerides, mg/dL	122 (90.8-164.2)	108 (80-145)	159 (114-199)	142 (106-204)
ALT, U/L	30.5 (20-41)	32 (22-46)	26 (21-35)	22.1 (16.7-30)
AST, U/L	26 (22-32)	29 (24-36)	23 (19-27)	24.8 (21.3-29.2)
GGT, U/L	25 (17.5-34)	31 (20-52)	23 (17-32)	28.2 (19.9-42.8)
Bilirubin, mg/dL	0.5 (0.4-0.7)	-	-	0.5 (0.4-0.6)
Albumin, g/dL	4.2 (0.3)	3.8 (0.4)	-	4.5 (0.3)
Platelets, 10e3/uL	282.7 (63.4)	252.7 (63.0)	234.7 (51.5)	250.8 (56.6)
Hypertension, n (%)	109 (41%)	232 (63%)	699 (74%)	2,236 (42%)
Type 2 diabetes, n (%)	41 (16%)	141 (38%)	35 (4%)	405 (8%)

Continuous variables are shown as mean (SD) or median (IQR) as appropriate. Categorical variables are shown as number (percentage).

Bootstrapping stepwise regression
(2000 boots)

Full Model

15 predictors: *age, gender, BMI, waist circumference, glucose, HbA1c, total cholesterol, HDL cholesterol, triglycerides, AST, ALT, GGT, platelets, albumin, total bilirubin*

Final Model

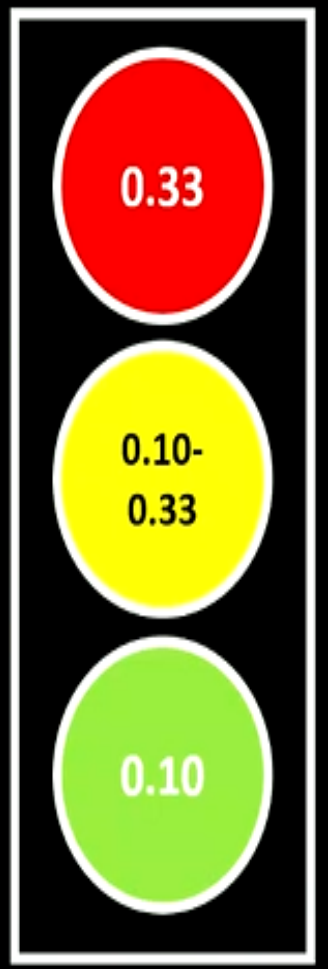
3 predictors: *AST, HbA1c, HDL cholesterol*

Fibrotic NASH Index (FNI)

$$FNI = \frac{e^{(-10.33+2.54\times\ln AST+3.86\times\ln HbA1c-1.66\times\ln HDL)}}{1+e^{(-10.33+2.54\times\ln AST+3.86\times\ln HbA1c-1.66\times\ln HDL)}}$$

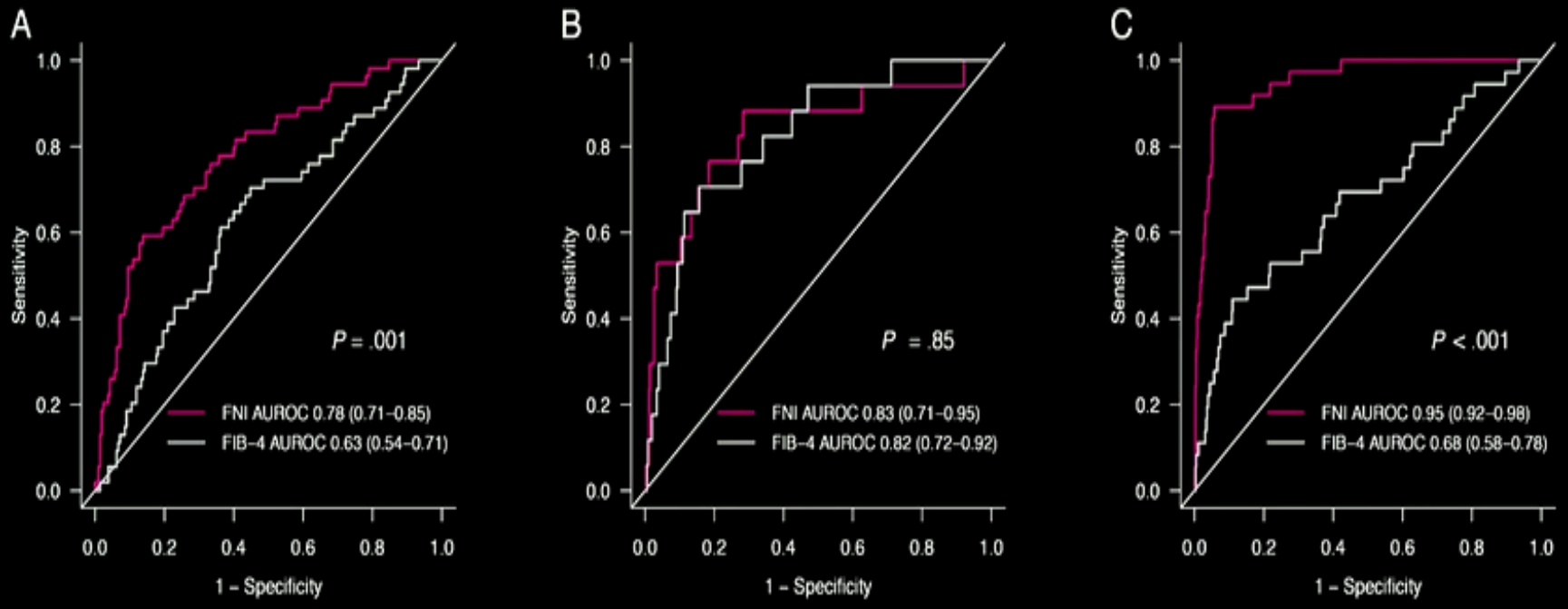
FNI cut-offs for fibrotic NASH

	MAFALDA	Helsinki	Liver Bible	MRI UK Biobank
N	264	370	947	5,368
Fibrotic NASH, n (%)	54 (20%)	17 (5%)	37 (4%)	118 (2%)
FNI AUROC (95% CI)	0.78 (0.71-0.85)	0.83 (0.72-0.95)	0.95 (0.92-0.98)	0.80 (0.75-0.83)
FNI ≤0.10 (Rule-out zone)				
n (%)	83 (31.4%)	77 (20.8%)	464 (50%)	2,526 (47.1%)
Sensitivity	0.89	0.94	1	0.87
Specificity	0.37	0.22	0.51	0.54
PPV	0.27	0.06	0.08	0.04
NPV	0.93	0.99	1	0.99
FNI ≥0.33 (Rule-in zone)				
n (%)	49 (18.6%)	109 (29.4%)	41 (4.3%)	337 (6.3%)
Sensitivity	0.52	0.82	0.54	0.34
Specificity	0.90	0.73	0.98	0.94
PPV	0.57	0.13	0.49	0.12
NPV	0.88	0.99	0.98	0.98



FNI vs FIB-4

ROC curves for fibrotic NASH by FNI and FIB-4 in the (A) MAFALDA cohort (n=264), (B) Helsinki cohort (n=370), and (C) Liver Bible cohort (n=947)

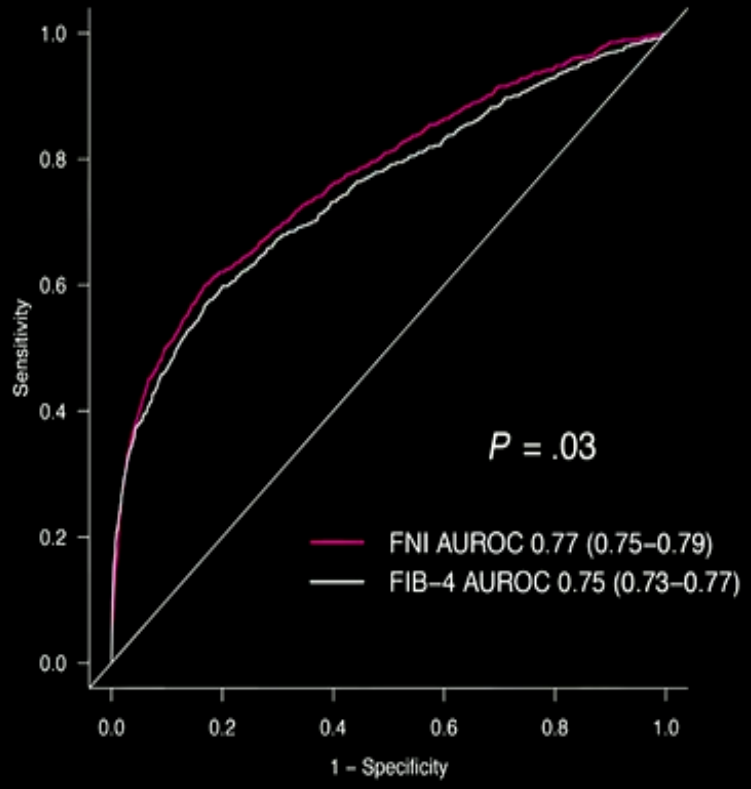


P values are calculated using the DeLong test. P values <0.05 are considered statistically significant.

AUROC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4 index; FNI, fibrotic NASH index.

Prediction of Severe Liver Disease

ROC curves for incident severe liver disease by FNI and FIB-4 in the UK Biobank (n=305,745)

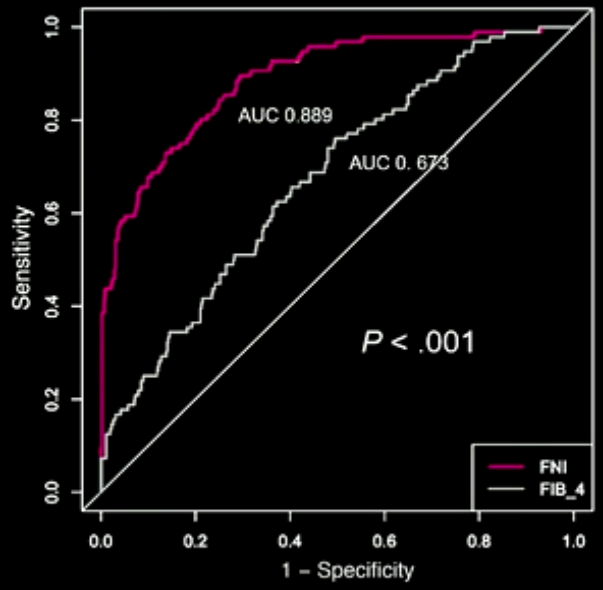


Performance was estimated by AUROC of Cox proportional hazards models.
P values are calculated using the DeLong test. P values <0.05 are considered statistically significant.

AUROC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4 index; FNI, fibrotic NASH index.

FNI in Type 2 Diabetes

ROC curves for fibrotic NASH by FNI and FIB-4 in individuals with type 2 diabetes (n=553)



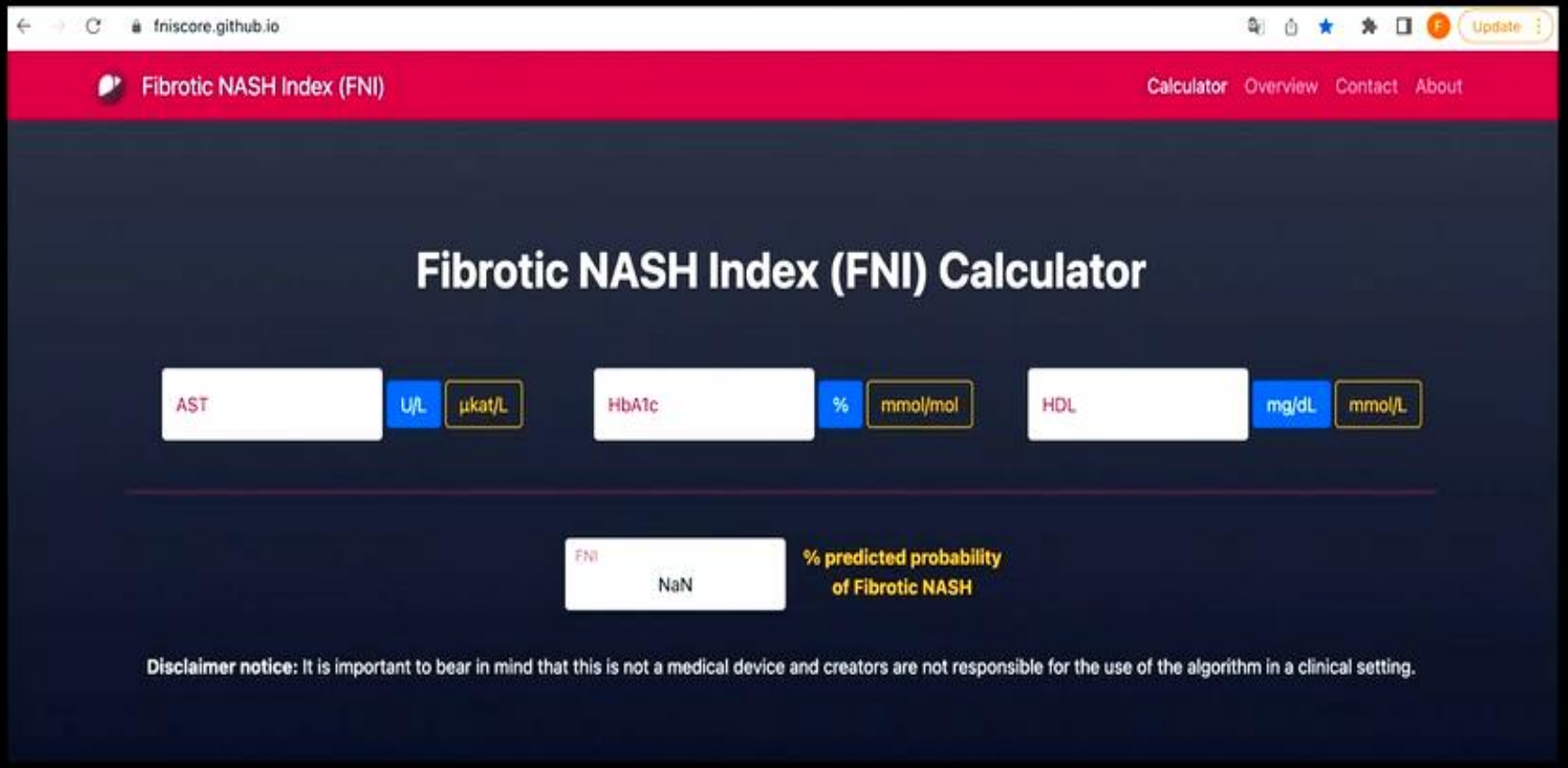
553 individuals with type 2 diabetes, 95 (17%) with fibrotic NASH. Fibrotic NASH defined as FAST score>0.35.

P values are calculated using the DeLong test. P values <0.05 are considered statistically significant.

AUC, area under the receiver operating characteristic curve; FAST, FibroScan-AST; FIB-4, Fibrosis-4 index; FNI, fibrotic NASH index.

Pina, Meneses et al. Liver Int. 2022

FNI can be easily calculated on the following website:
https://fniscore.github.io/

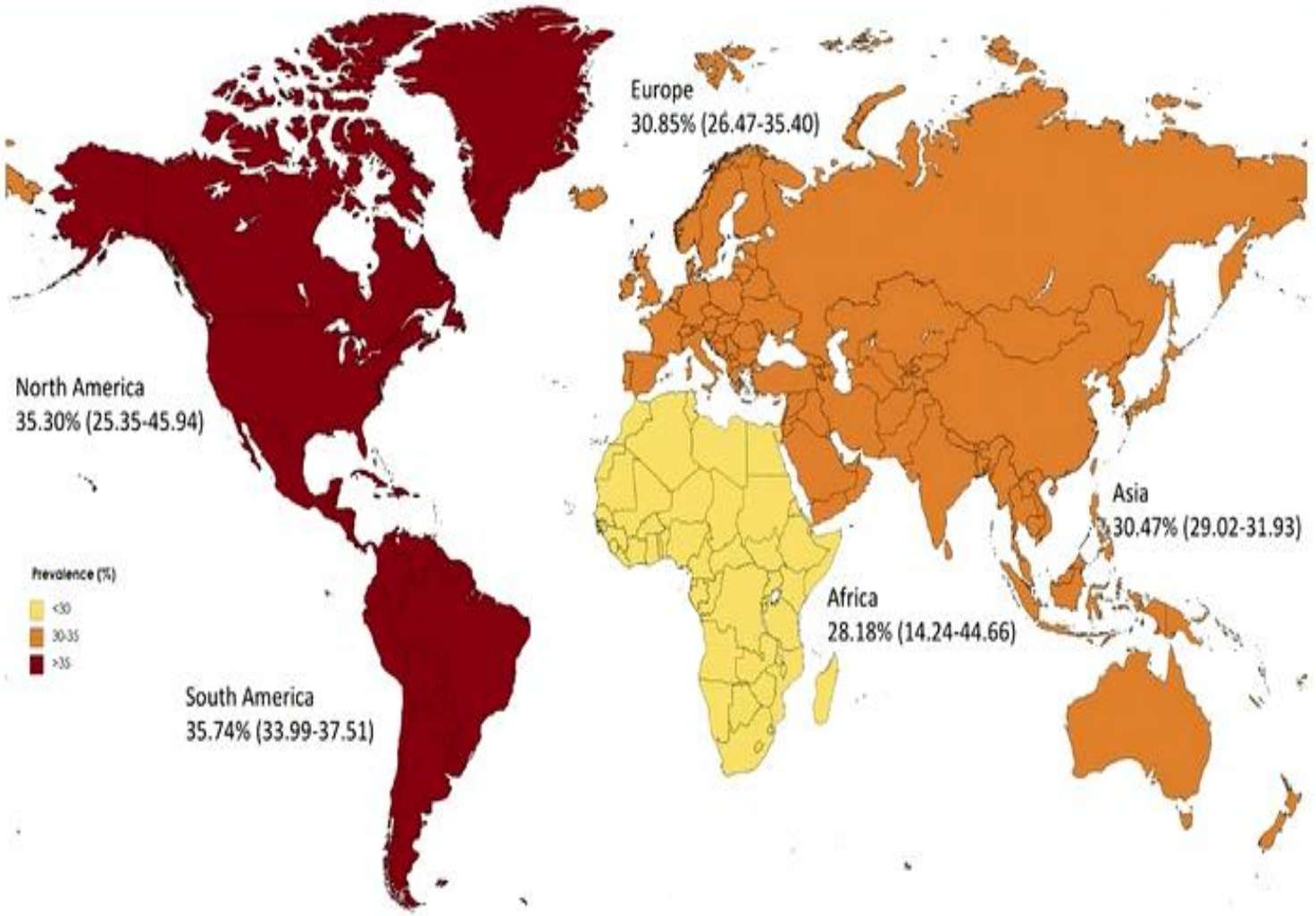


Conclusions

- FNI is the first score for fibrotic NASH based on routine laboratory tests, namely AST, HDL cholesterol, and HbA1c.

- FNI may represent an accurate, simple, and affordable non-invasive tool to screen for fibrotic NASH in high-risk individuals in primary healthcare and diabetology/endocrinology clinics.

NAFLD is a global issue



Clin Gastroenterol Hepatol. 2021.

A-22-951-EASD

Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: A randomized controlled trial (ESSENTIAL study)

Youngjoon Kim, Yongin Cho, Hyungjin Rhee, Young-eun Kim, Minyoung Lee, Byung-Wan Lee, Eun Seok Kang, Bong-Soo Cha, Jin-Young Choi, Yong-ho Lee

Severance Hospital
Department of Internal Medicine,
Yonsei University College of Medicine,
Seoul, Korea

Youngjoon Kim
Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: a randomised controlled trial (ESSENTIAL study)

Benefit in using statin in patients with NAFLD is limited

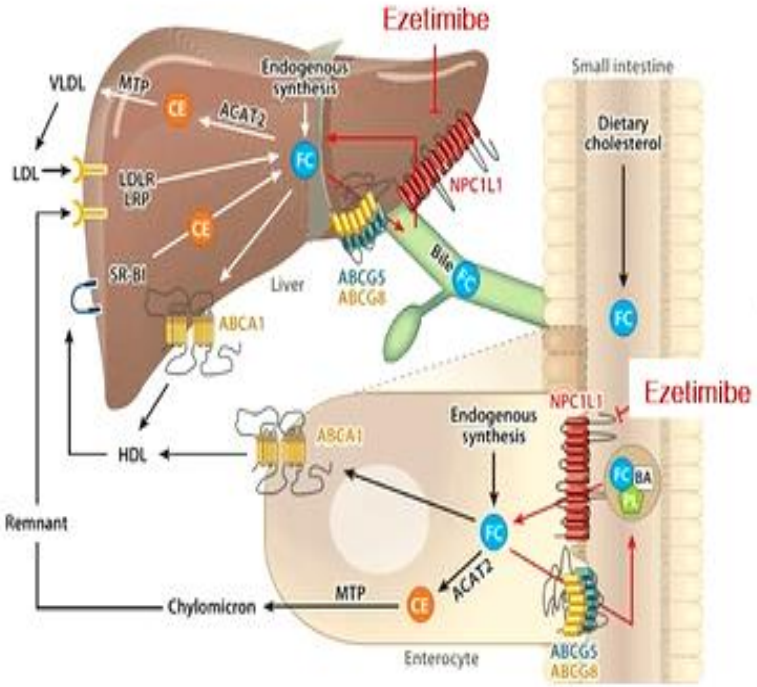
	Simvastatin (n = 10)		
Variable	Before Treatment	After Treatment	*P*
Aspartate aminotransferase (U/L)	43.3 ± 14.8	36.5 ± 11.5	NS
Alanine aminotransferase (U/L)	70.4 ± 29.6	49.5 ± 15.6	NS
Grade (necroinflammatory activity)	1.4 ± 0.5	1.4 ± 0.5	NS
Stage (fibrosis)	1.25 ± 0.7 (1-3)	1.50 ± 0.9 (1-3)	NS
% Steatosis	25 ± 14.7 (5-50)	23.8 ± 21.2 (5-60)	NS
Total cholesterol (mg/dL)	230.5 ± 72.5	209.1 ± 114.7	NS
Low-density lipoprotein (mg/dL)	138.5	102.7	NS
Triglycerides (mg/dL)	388.7 ± 507.9	490.0 ± 890.5	NS
Alkaline phosphatase (IU/L)	86.1 ± 30.9	89.7 ± 23.2	NS
Body mass index (BMI)	37.3	35.1	NS

J Clin Gastroenterol. 2009 Nov-Dec;43(10):990-4.

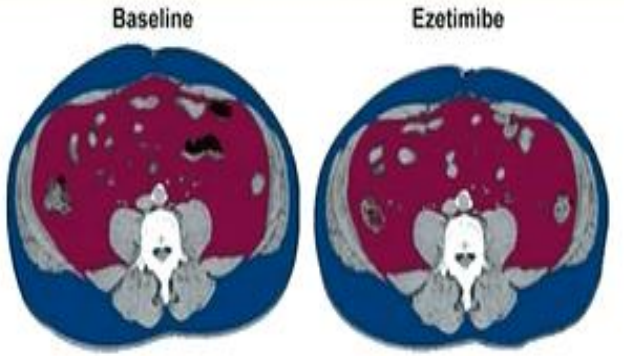
Characteristics	Cases (n = 164,856) n (%)	Controls (n = 824,280) n (%)	Adjusted OR (95% CI)[b]
Statin use			
Never use	142,135 (86.2)	673,958 (81.6)	1.00
Ever use	22,721 (13.8)	151,322 (18.4)	0.66 (0.65–0.67)
Cumulative dose of use			
Never use	142,135 (86.2)	672,958 (81.6)	1.00
Ever use			
≤90 cDDDs	13,732 (8.3)	84,396 (10.2)	0.79 (0.77–0.81)
91–365 cDDDs	4,700 (2.8)	24,040 (2.9)	0.82 (0.79–0.85)
366–730 cDDDs	2,185 (1.3)	14,856 (1.8)	0.58 (0.55–0.61)
>730 cDDDs	2,104 (1.3)	28,030 (3.4)	0.28 (0.27–0.29)

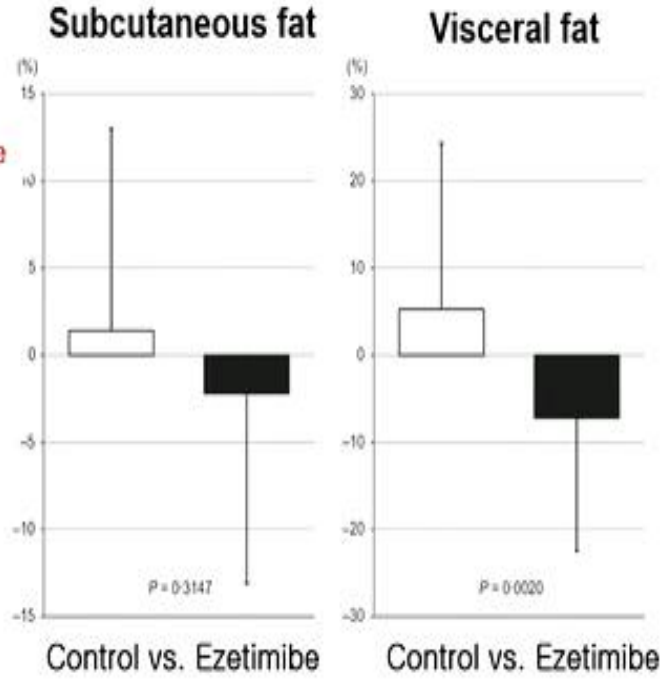
Am J Gastroenterol. 2021 Jan 1;116(1):116-124

Ezetimibe reduces visceral fat



Annu. Rev. Physiol. 2011. 73:239–59





Eur J Clin Invest. 2012 Dec;42(12):1287-94

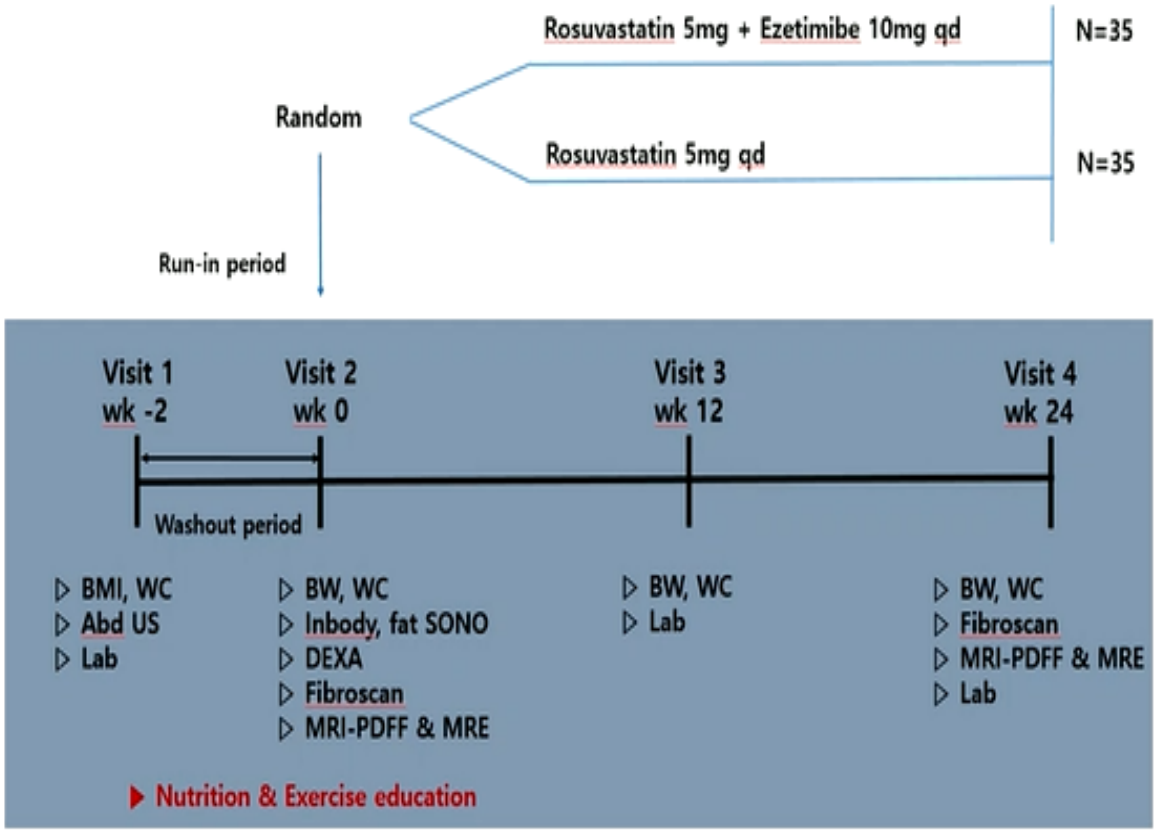
Objectives

1. To assess change in liver fat by MRI-PDFF in patients with non-alcoholic fatty liver disease(NAFLD) on ezetimibe combination therapy with statin.

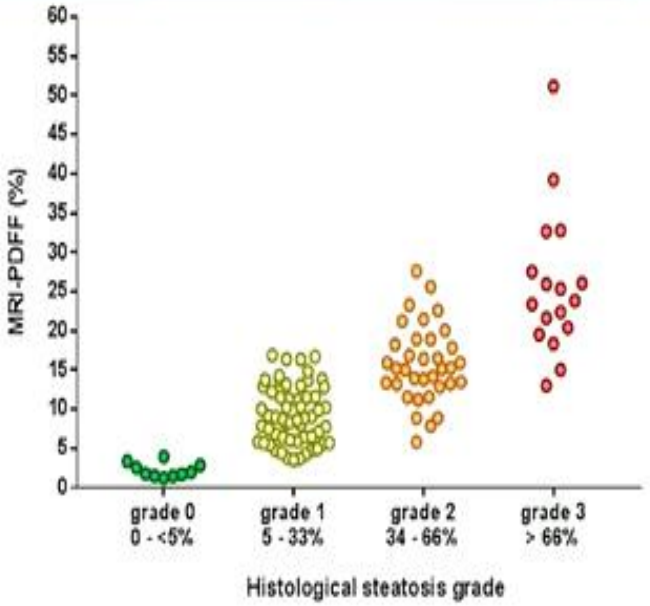
2. To investigate whether ezetimibe contributes to hepatic steatosis improvement in the setting of controlled statin treatment.

Study Design and Patient Population

Design: an investigator-initiated, randomized, open-label, prospective, active-controlled clinical trial
Patient population: **70** Participants recruited from Severance Hospital from May 2018 to June 2019 in Seoul, Korea
Study duration: 24weeks
Primary outcome: change in liver fat by MRI-PDFF

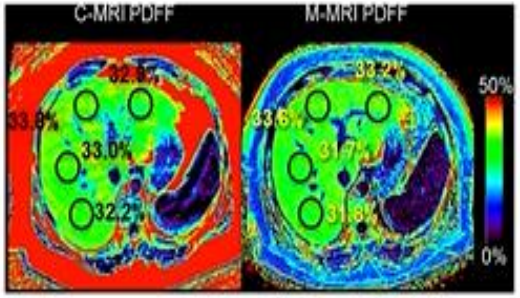


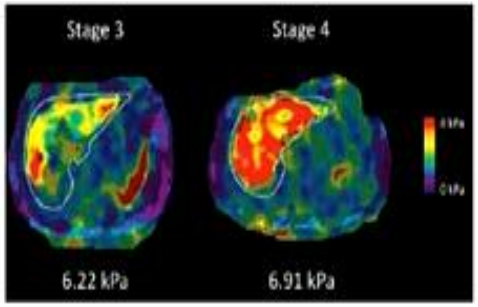
MRI-PDFF & MRE



Magnetic resonance imaging derived proton density fat fraction(MRI-PDFF)

Magnetic resonance elastography(MRE)





Hepatology. 2018 Aug; 68(2): 763–772.

Hepatology. 2014 Dec; 60(2): 1920-1928.

Baseline Demographics

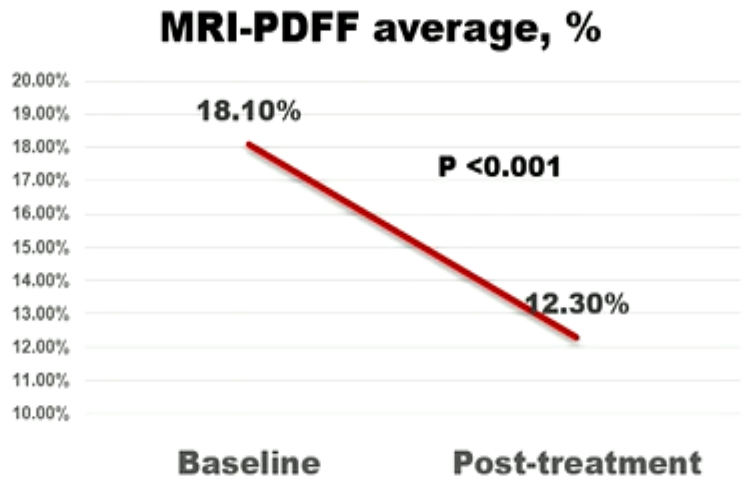
	Ezetimibe + Rosuvastatin (n=34)	Rosuvastatin alone (n=36)	P-value
Age, years	50.3(12.9)	52.5(19.1)	0.647
Female, n (%)	12(35.3)	18(50.0)	0.214
Weight, kg	78.2(19.3)	77.2(15.5)	0.958
BMI, kg/m^2	27.7(6.6)	28.6(3.6)	0.196
Waist circumference, cm	95.0(15.3)	96.5(11.1)	0.685
Presence of diabetes, n(%)	26(72.2)	26(76.5)	0.684

Baseline biochemical characteristics

	Ezetimibe + Rosuvastatin (n=34)	Rosuvastatin alone (n=36)	P-value
ALT, IU/l	37.5(30.0)	30.0(22.0)	0.099
AST, IU/l	24.5(13.0)	24.5(13.0)	0.706
Alk Phos, U/l	64.0(22.0)	68.5(36.0)	0.121
GGT, U/l	42.5(36.0)	35.0(33.0)	0.347
Glucose, mg/dl	116.0(26.0)	114(35.0)	0.958
Insulin, uU/ml	12.4(10.3)	14.7(9.1)	0.171
Hba1c, %	6.4(0.5)	6.4(0.9)	0.548
HOMA-IR	3.5(3.5)	3.9(2.7)	0.166
Triglycerides, mg/dl	176.5(143.0)	217(159.0)	0.177
LDL, mg/dl	115.3(64.7)	111.2(39.9)	0.742

Ezetimibe plus rosuvastatin vs. rosuvastatin monotherapy: longitudinal changes in hepatic steatosis and fibrosis

		Ezetimibe + Rosuvastatin (n=34)			Rosuvastatin alone (n=36)		Difference between groups
	Baseline	Post-treatment	P-value	Baseline	Post-treatment	P-value	P-value
MRI-PDFF average, %	18.1(8.2)	12.3(6.4)	<0.001	15.0(7.3)	12.4(7.4)	0.003	0.020
MRE, kPa	2.0(0.5)	2.1(0.5)	0.507	2.2(0.4)	2.2(0.7)	0.539	0.898



Changes in parameters after 24 weeks of treatment

	Ezetimibe + Rosuvastatin (n=34)			Rosuvastatin alone (n=36)			Difference between groups
	Baseline	Post-treatment	P-value	Baseline	Post-treatment	P-value	P-value
BMI, kg/m^2	26.6(6.4)	26.2(5.8)	0.002	28.3(3.6)	27.9(3.7)	0.001	0.675
Waist circumference, cm	94.0(15.0)	91.0(13.0)	<0.001	96.0(12.5)	93.5(14.0)	<0.001	0.269
ALT, IU/l	40.0(31.0)	40.0(24.0)	0.459	31.0(21.0)	32.0(26.0)	0.563	0.471
AST, IU/l	25.0(14.0)	26.0(15.0)	0.681	24.0(11.0)	27.0(18.0)	0.727	0.462
Alk Phos, U/l	64.0(21.0)	63.0(18.0)	0.642	71.0(36.0)	70.0(32.5)	0.326	0.510
GGT, U/l	43.0(35.0)	32.0(41.0)	0.125	36.0(33.5)	33.0(27.5)	0.957	0.861

Changes in parameters after 24 weeks of treatment

	Ezetimibe + Rosuvastatin (n=34)			Rosuvastatin alone (n=36)			Difference between groups
	Baseline	Post-treatment	P-value	Baseline	Post-treatment	P-value	P-value
Glucose, mg/dl	116.0(29.0)	116.0(40.0)	0.378	115.0(33.5)	120.0(25.0)	0.957	0.345
Insulin, uU/ml	12.5(9.3)	12.7(6.9)	0.931	15.0(8.0)	15.5(12.1)	0.993	0.911
Hba1c, %	6.4(0.6)	6.5(0.8)	0.167	6.4(1.1)	6.5(1.4)	0.055	0.445
HOMA-IR	3.6(3.7)	3.5(3.0)	0.814	4.0(3.5)	4.7(3.3)	0.925	0.691
Triglycerides, mg/dl	177.0(139.0)	138.0(77.0)	<0.001	217.0(157.0)	135.0(71.0)	<0.001	0.175
LDL, mg/dl	116.0(66.4)	55.0(37.2)	<0.001	109.8(42.9)	66.4(28.3)	<0.001	0.111
CRP, mg/l	1.4(1.7)	0.8(1.2)	0.036	1.5(1.4)	0.8(1.6)	0.008	0.805
IL-18, pg/ml	163.6(73.8)	146.2(52.0)	0.003	168.2(73.8)	162.6(76.8)	0.042	0.210

Limitations

1. Marginally imbalanced hepatic steatosis at the baseline
2. Liver biopsy was not performed
3. Small sample size and short intervention period

Strengths

1. Used MRI-PDFF, which is highly reliable method of assessing hepatic steatosis.
2. Investigated the effect of combination therapy, which is widely prescribed in the clinical environment.
3. Identified characteristics of participants in whom ezetimibe acted more effectively

Conclusions

- The use of ezetimibe in combination with rosuvastatin significantly improved hepatic steatosis in patients with NAFLD.

- Individuals with higher BMI, T2DM, insulin resistance, and severe liver fibrosis were likely to be good responders to ezetimibe treatment.

- These data indicate that ezetimibe plus rosuvastatin is a safe and effective therapeutic option to treat patients with NAFLD and dyslipidemia