2019 12th Paris Hepatology Conference
PHC 2019
14 & 15 January 2019
PARIS - Palais des Congrès

Clinical Case

Ana Carolina Cardoso, MD
Federal University of Rio de Janeiro - Brazil

2019 12th Paris Hepatology Conference
PHC 2019
14 & 15 January 2019
PARIS - Palais des Congrès

Disclosures

Nothing to declare

- A 55-year-old female, asymptomatic, underwent abdominal ultrasound that revealed severe steatosis.

- Hypertension - use of losartan.

- 5-year history of type 2 diabetes - use of Metformin.

- Alcohol use on weekends.

- Obstetrical history: two deliveries and one miscarriage.

- Her pregnancies occurred before the diagnosis of diabetes.

- She had gestational diabetes.

- She does not know the birth weights of her children.

- Family history: positive for diabetes (mother).

- **Physical exam:**

  Height: 1.60 m, Weight: 93 kg (BMI = 36.3 Kg/m2)

  Mild acanthosis nigricans

  Abdomen – Hepatomegaly.

  No retinopathy and/or evidence of neuropathy.

- **Lab Results**

Platelets: 170.000
Glucose: 158 mg/dl (65-109 mg/dl); A1C: 6.6% (normal: 4-6%)
Creatinine: 1.0 mg/dl (0.5-1.4 mg/dl)
Urea nitrogen: 18 mg/dl (7-30 mg/dl)
Albumin: 4,0 g/L
ALT: 24 IU/l (5-40 IU/l)
AST: 19 IU/l (5-40 IU/l)
Negative viral markers and auto antibodies

- **Evaluation**

FIB-4: 1.25 – Fibrosis stage 0-1

NAFLD Fibrosis Score: - 2.204 - < F2

A) Should I wait high aminotransferases to investigate NASH?

B) Should I perform liver biopsy? Because it is a patient with the possibility of presenting steatohepatitis

C) Should I perform Transient Elastography?

D) Lifestyle-modifying measures and repeat ultrasound in 6 months?

E) Initiation of liraglutide as an obese and diabetic patient probable with steatohepatitis

A) Should I wait high aminotransferases to investigate NASH?

B) Should I perform liver biopsy? Because it is a patient with the possibility of presenting steatohepatitis

C) Should I perform Transient Elastography?

D) Lifestyle-modifying measures and repeat ultrasound in 6 months?

E) Initiation of liraglutide as an obese and diabetic patient with probable steatohepatitis

- 6 months later...

Physical exam: Weight 96 kg (BMI = 37.5 Kg/m2).

Abdominal ultrasound - severe steatosis and hepatomegaly.

- Lab Results

Platelets: 158.000

Glucose: 190 mg/dl (65–109 mg/dl); A1C: 7.2% (normal: 4–6%)

ALT: 22 IU/l (5–40 IU/l)

AST: 20 IU/l (5–40 IU/l)

Albumin 3,8 g/L

- **Evaluation**

NAFLD Fibrosis Score: -2.04 - < F2

FIB – 4: 1.48 – F2- F3

A) Should I wait high aminotransferases to investigate NASH?

B) Should I perform liver biopsy?

C) Should I perform Transient Elastography?

D) Reinforce lifestyle-modifying measures and repeat ultrasound in 6 months?

E) Initiate liraglutide?

- **Transient elastography**

XL probe: 10,3 kPa/ IQR 18%/ SR 100%/ CAP 350 dB/m/ IQR 40 – F3

A) Should I perform liver biopsy?

B) Should I repeat TE/ FIB-4/ NAFLD in 6 months? In a year?

C) Reinforce lifestyle-modifying measures and repeat ultrasonography in 6 months?

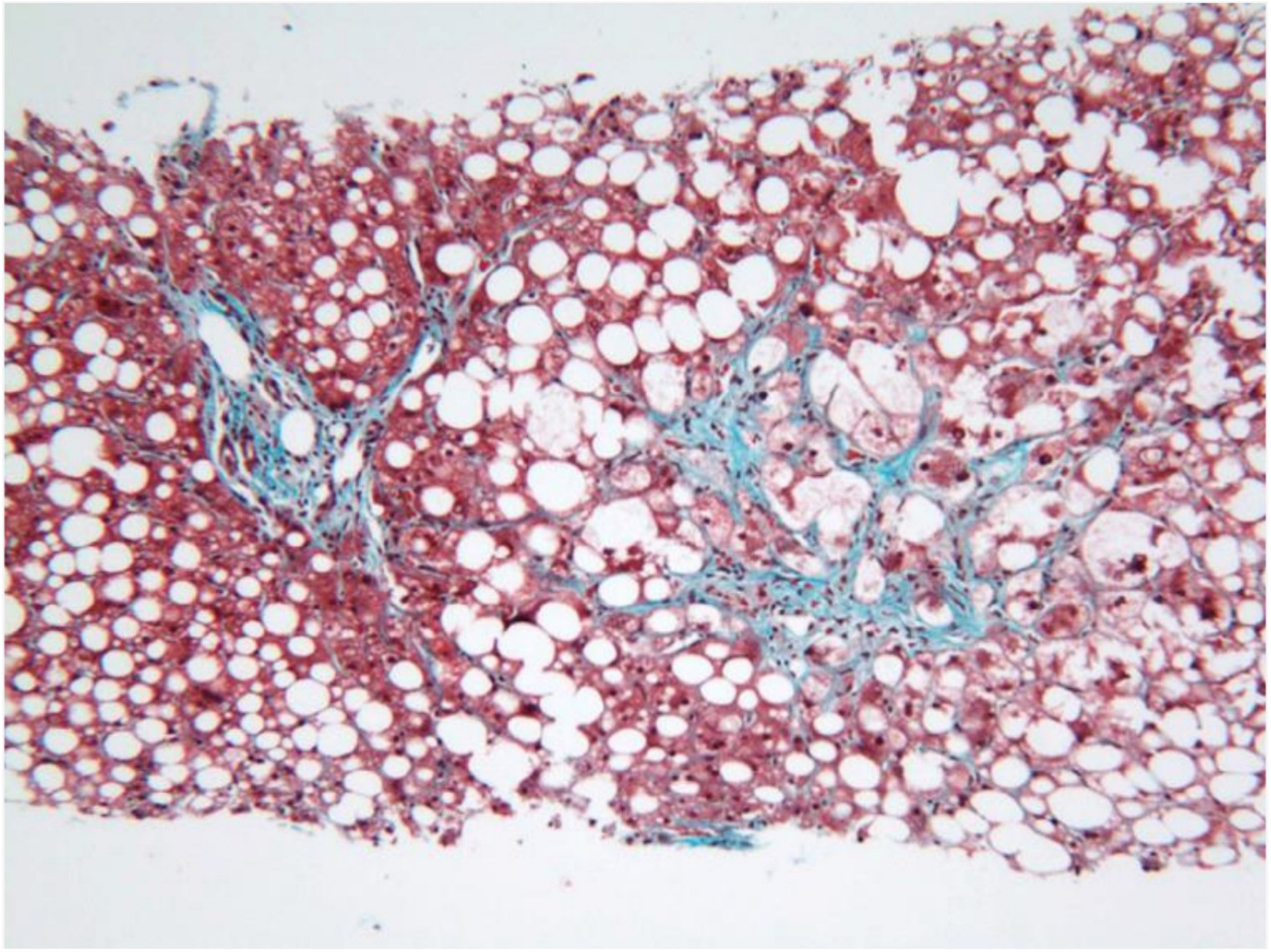
D) Initiation of liraglutide (GLP 1) or other medication (Pioglitazone/ Vitamin E)?

2019 12th PARIS HEPATOLOGY CONFERENCE

PHC 2019

14 & 15 January 2019

PARIS - Palais des Congrès



A) Continue to follow with TE and lifestyle modification?

B) Start vitamin E and new evaluation at 6 months with TE?

NAFLD? FIB-4?

C) Start pioglitazone and new evaluation at 6 months with TE?

NAFLD? FIB-4?

Liver and diabetes
Cause or consequence?

Nonalcoholic fat liver disease increase the risk of type 2 DM?

- ✓ Up to 70% of patients with NAFLD have glucose intolerance and/or DM when submitted to a glucose tolerance test.

(Willner et al. Am J Gastroenterol. 2001; Ortiz-Lopez et al. Diabetes Care. 2012)

- ✓ 3 meta-analyzes (40, 20 and 19 studies included)
- ✓ Patients with diagnosis of NAFLD by image (lack of studies with LB)
- ✓ ↑ 2X the risk of DM2
- ✓ Follow-up: 4 to 10 years.

(Musso et al. Ann Med. 2011; Ballestri et al. J Gastroenterol Hepatol 2016; Mantovani A et al. Diabetes Care 2018)

Prevalence of NASH/ Advanced Fibrosis DM2

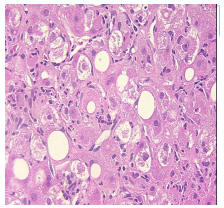
SAT-525

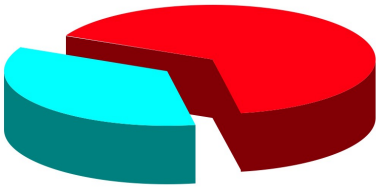
The worldwide prevalence of Non-alcoholic Steatohepatitis (NASH) in patients with Type 2 Diabetes Mellitus (DM)

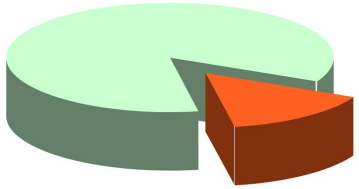
P. Golabi[1], J. Paik[1], L. Deavila[1], N. Fukui[2], M. Srishord[1], Z. Younossi[3].
[1]Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States; [2]Inova Fairfax Hospital, Center for Liver Disease, Department of Medicine, Falls Church, United States; [3]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States

Meta-analysis (2003-2014)

N= 27020 DM2 patients







DM accelerates progression to fibrosis and increases risk of clinical events

- ✓ In longitudinal studies with reevaluation of histology, DM was a risk factor for progression of fibrosis in NAFLD

Adams et al Gastroenterology 2005; Ekstedt et al. Hepatology 2006;

- ✓ There is a higher mortality from cardiovascular events and complications related to chronic liver disease in patients with NAFLD and DM

Rafiq et al. Clin Gastroenterol Hepatol. 2009; Targer et al. Diabetes Care. 2007, Stepanova et al. Dig Dis Sci. 2013, Björkström K et al. Abstract 2018 -EASL

What is the role of ALT and/or AST in the diagnosis of NASH and fibrosis in DM2 patients?

- ✓ In patients with DM2 and steatohepatitis aminotransferases were elevated only in 15-38%.

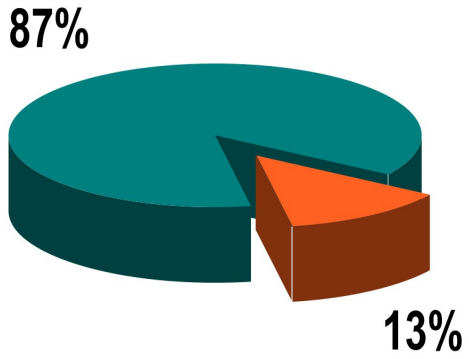
Leite et al. Liver Int 2011; Prashanth M et al. J Assoc Physicians India 2009.

- ✓ Repeatedly normal ALT and/or AST do not exclude higher degrees of inflammatory activity or advanced stages of fibrosis.

Leite et al. Liver Int 2011; Williamson RM. QJM 2012;
Portillo Sanchez P et al. J Clin Endocrinol Metab 2015;
Sandler D et al. Abstract 2018 -EASL.

Evaluation of fibrosis in our cohort of diabetics with NAFLD

- 303 exams
- 61% female; 59 ± 9 years.
- BMI: 31 ± 5 Kg/m2



ies with TE found
alences between 7.3 and
% of advanced fibrosis.

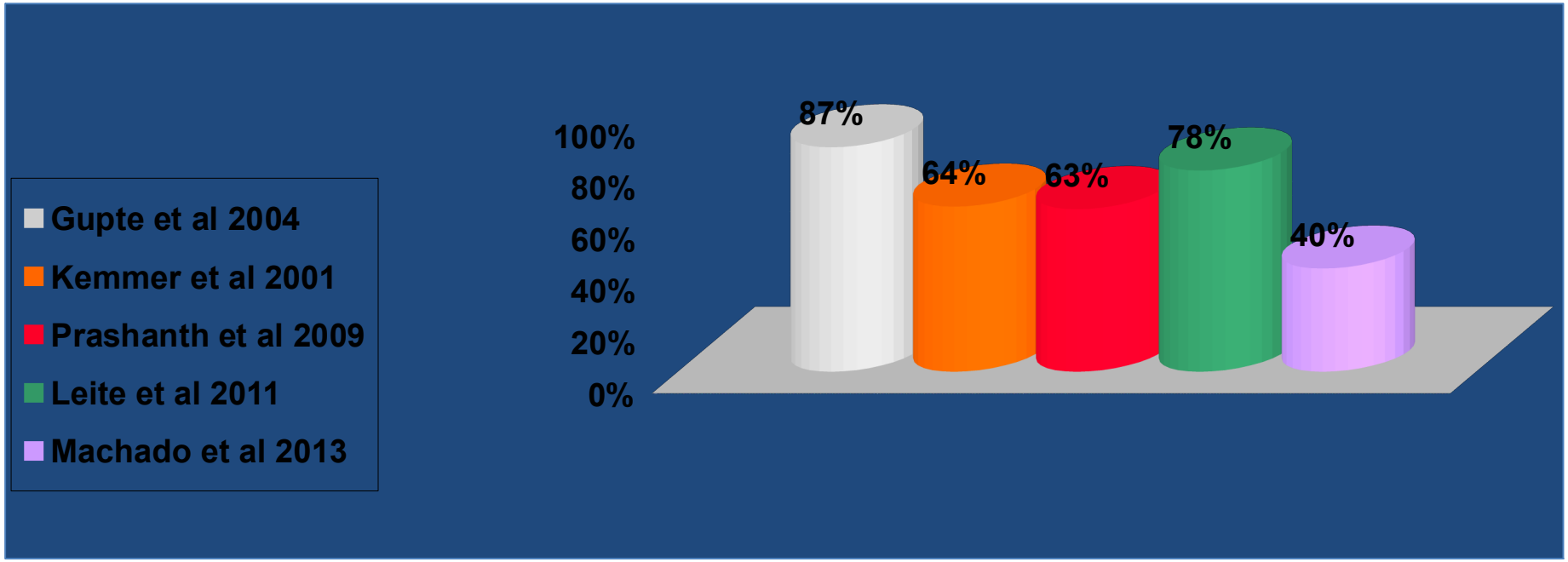
a I et al J Gastrointestin Liver Dis.

et al. Gut 2015;

D et al. Liver Int 2017)

DHGNA/ *NASH*/ DM2

Esteatohepatite avaliada através da biópsia hepática



- Casuística entre 32 e 92 pacientes.
- Tempo de Diabetes de 7 a 8 anos.
- Aminotransferases elevadas de 15 a 38% dos pacientes.

NAFLD Fibrosis Score
Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years) ☐
BMI (kg/m2) ☐

IGF/diabetes ☐

AST ☐
ALT ☐
Platelets (x109/l) ☐
Albumin (g/l) ☐

- ✓ **NAFLD fibrosis Score:** Improves with ↑ age, BMI, GI or DM and AST/ALT and ↓ de platelets and albumin.
- ✓ **< -1,455** associated with the **absence of advanced liver fibrosis.**
- ✓ **> 0,676** associated with the **presence of advanced liver fibrosis.**

Angulo et al. Hepatology 2007

NAFLD Fibrosis Score

Table 4. Predictive Value of the Scoring System Obtained from the Validation Group (n = 253)

	Low Cutoff Point (< −1.455)	Indeterminate (−1.455-0.676)	High Cutoff Point (>0.676)	Total
Total	144	70	39	253
No significant fibrosis (stage 0-2)	127	45	7	179
Significant fibrosis (stage 3-4)	17	25	32	74
Sensitivity	77%		43%	
Specificity	71%		96%	
Positive predictive value	52%		82%	
Negative predictive value	88%		80%	
Likelihood ratio (+)	2.652		11.058	
Likelihood ratio (−)	0.324		0.591	
Interpretation	Absence of significant fibrosis (88% certainty)		Presence of significant fibrosis (82% certainty)	

NOTE. Prevalence of advanced fibrosis of 29% in the validation group.

Angulo et al. Hepatology 2007

FIB - 4

$$\text{FIB - 4} = \frac{\text{Age (Years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (109/L)} \times \sqrt{\text{ALT (U/L)}}}$$

F ≥ 3

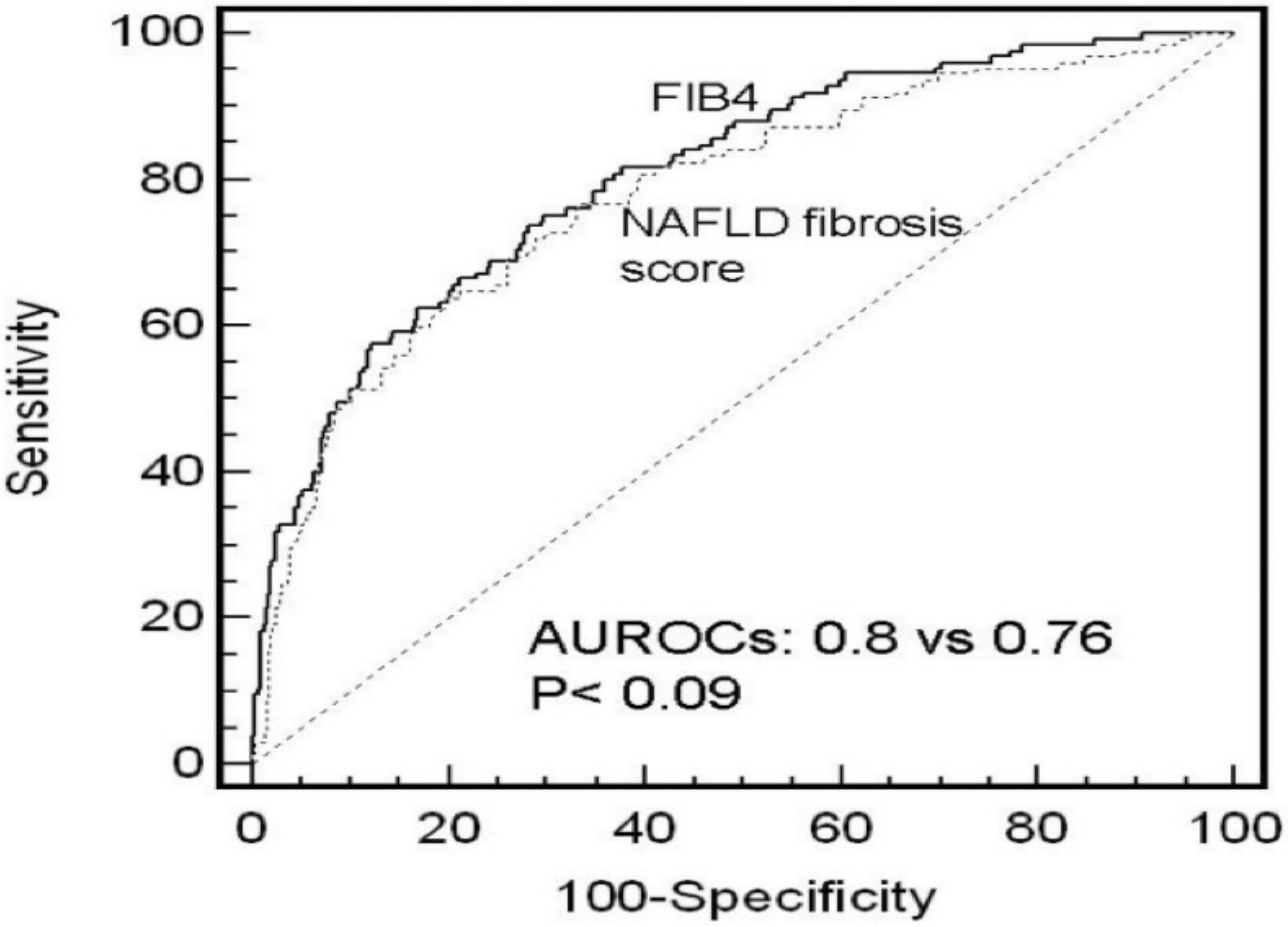
Cut-off	SEN	ESP	VPP	VPN
≤ 1,45	80%	74%	39%	95%
Zona cinza				
≥ 3,25	38%	98%	82%	88%

N= 847
HCV

Vallet-Pichard et al. Hepatology 2007

FIB - 4

F ≥ 3

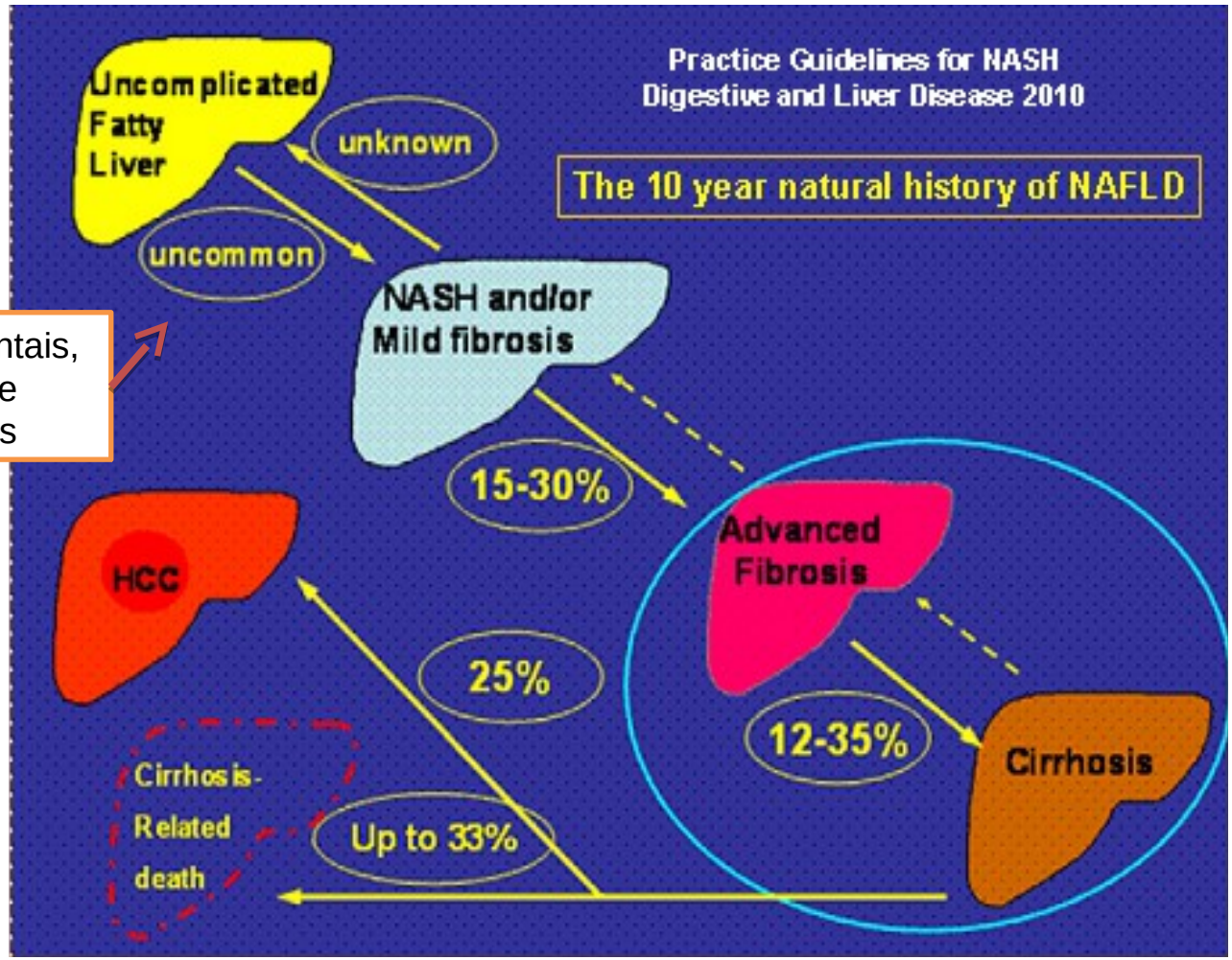


Shah et al.Clin Gastroenterol Hepatol 2009

UFRJ

Historia Natural da DHGNA

Fatores Ambientais, Genéticos e Metabólicos



UFRJ

Introdução - Biópsia hepática (BH)

- Padrão ouro
- 1/50.000 volume hepático
- Atividade /Fibrose
- Esteatose
- Lesões associadas

+ Método invasivo
+ Custo
+ Morbimortalidade
+ Erros de amostragem
+ Variabilidade intra e inter-observador
+ Não permite avaliações frequentes

Regev et al. Am J Gastroenterol 2002; 97:2614-8
Bedossa et al. Hepatology 2003;38: 1449-57
Rousselet et al. Hepatology 2005; 41: 257-64

UFRJ

Introdução

- Fibrose avançada, determinada por marcadores não invasivos, foi preditora de complicações relacionadas ao fígado e mortalidade.
- Estudos asiáticos e ocidentais evidenciaram que pacientes com síndrome metabólica e diabetes (DM2) apresentam maior risco de desenvolver fibrose.

Angulo P, et al. Gastroenterology 2013
Kim D, et al. Hepatology 2013
Farrell, et al. Nat Rev Gastroenterol Hepatol 2013
Dixon, et al. Gastroenterology 2001

UFRJ

Introdução – Esteatose
o diagnóstico é útil?

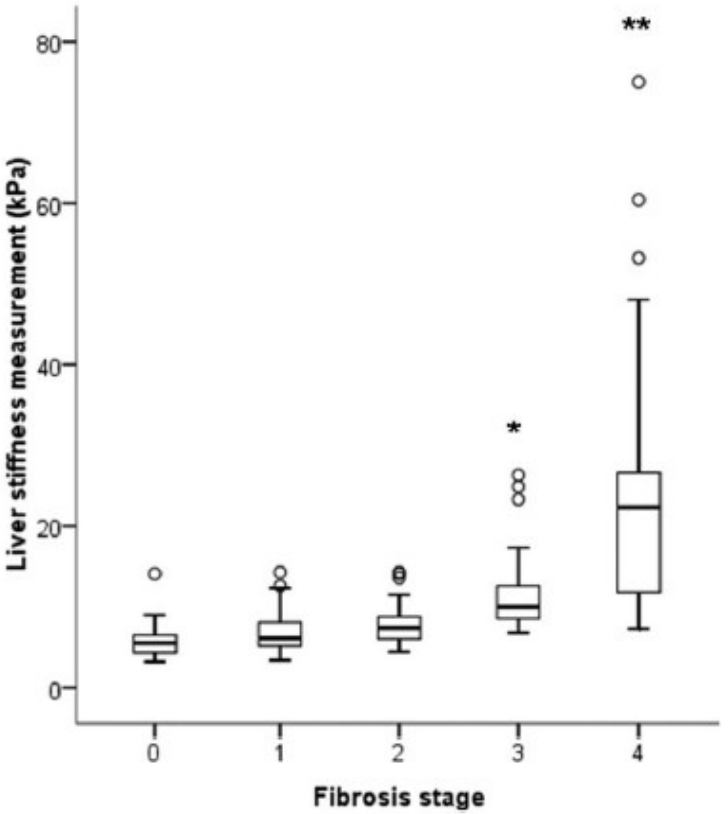
- Freqüentemente é o que identifica o paciente como portador de DHGNA.
- Associada a outras condições (DM, DCV, HAS).
- Ultrassonografia é o método mais utilizado – padrão ouro RNM (custo efetivo, fácil acesso *vs*. limitações no IMC> 40 e esteatose leve).
- Quantificação da esteatose pode ser importante no seguimento das intervenções terapêuticas.

UFRJ

Diagnóstico da DHGNA através EHT

n = 246

- F0/F1 ≤ 5,5 kPa
- F1 – 5,6 kPa
- F2 – 7,1 kPa
- F3 – 9,6 kPa (VPP – 72%; VPN – 93%)
- F4 > 20 kPa
- F4 – 10,3 kPa (VPP – 46% e VPN – 99%)



Wong, et al. Hepatology 2010

UFRJ

Diagnóstico de esteatose através do CAP

n = 115

Table 2 Area under ROC curve (AUROC) for the detection of steatosis (S) ≥ S1 (≥ 11%), ≥ S2 (≥ 34%), = S3 (≥ 67%) using controlled attenuation parameter (CAP) and diagnosis performance for the optimal cut-off value (maximum Youden index) in $dB.m^{-1}$: Sensibility (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV). Table adapted from reference [7].

	S ≥ S1 (≥ 11%)	S ≥ S2 (≥ 34%)	S = S3 (≥ 67%)
AUROC	0.91 (0.86~0.97)	0.95 (0.91~1)	0.89 (0.75~1)
Optimal cut-off	238	259	292
Se	0.91 (0.86~0.96)	0.89 (0.82~0.96)	1 (1~1)
Sp	0.81 (0.74~0.89)	0.86 (0.78~0.93)	0.78 (0.60~0.97)
PPV	0.87 (0.81~0.94)	0.80 (0.71~0.89)	0.28 (0.13~0.43)
NPV	0.87 (0.80~0.93)	0.92 (0.87~0.98)	1 (1~1)

Sasso, et al. Clin Res Hepatol Gastroenterol 2010