MTX Induced Liver Injury and Noninvasive Markers of Fibrosis

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Objectives

- Discuss MTX Induced Liver Injury
  - Pathophysiology
  - Prevalence
  - Risk Factors
  - Guidelines
- Discuss Noninvasive Markers of Fibrosis
  - Pathophysiology of fibrosis
  - Pros and Cons of liver biopsy
  - Review recent data regarding noninvasive markers
  - Discuss noninvasive markers for MTX Induced Liver Injury and how they might change guidelines
- Discuss Current Research Ideas As They Apply To Above
- Try not to loose my fellowship in doing so.

Methotrexate

- Mechanism
  - Dihydrofolate reductase inhibitor
  - Blocks cell turnover
  - Decreases monocyte/neutrophil chemotaxis
  - Decreases leukotriene induced intra-epidermal penetration
- Indicated in 20% of all patients with psoriasis

MTX Liver Injury

- Methotrexate is the dominant systemic therapy for psoriasis (Efficacy >80%).
- Mechanism of injury?
  - Poorly understood= activation of HSC
  - Increased polyglutaminated MTX in hepatocytes
  - Inhibition of hepatic folate metabolism
  - Increased gut permeability

G. P. Aithal, B. Haugk, S. Das, T. Card, A. D. Burt, C. O. Record (2004) Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified?
Alimentary Pharmacology & Therapeutics 19 (4), 391–399.

MTX Liver Injury

- Up to 26 % of patients with psoriasis develop cirrhosis
  - Depends on cumulative dose (>4gm)
  - Depends on regimine (qweek vs other)
  - Depends on dose (>20mg/wk)
- Some people develop CLD more easily despite dose
  - EtOH consumption
  - Obese
  - Diabetic
- Up to 50% of pre-treatment biopsies are abnormal!
- Current Guidelines…

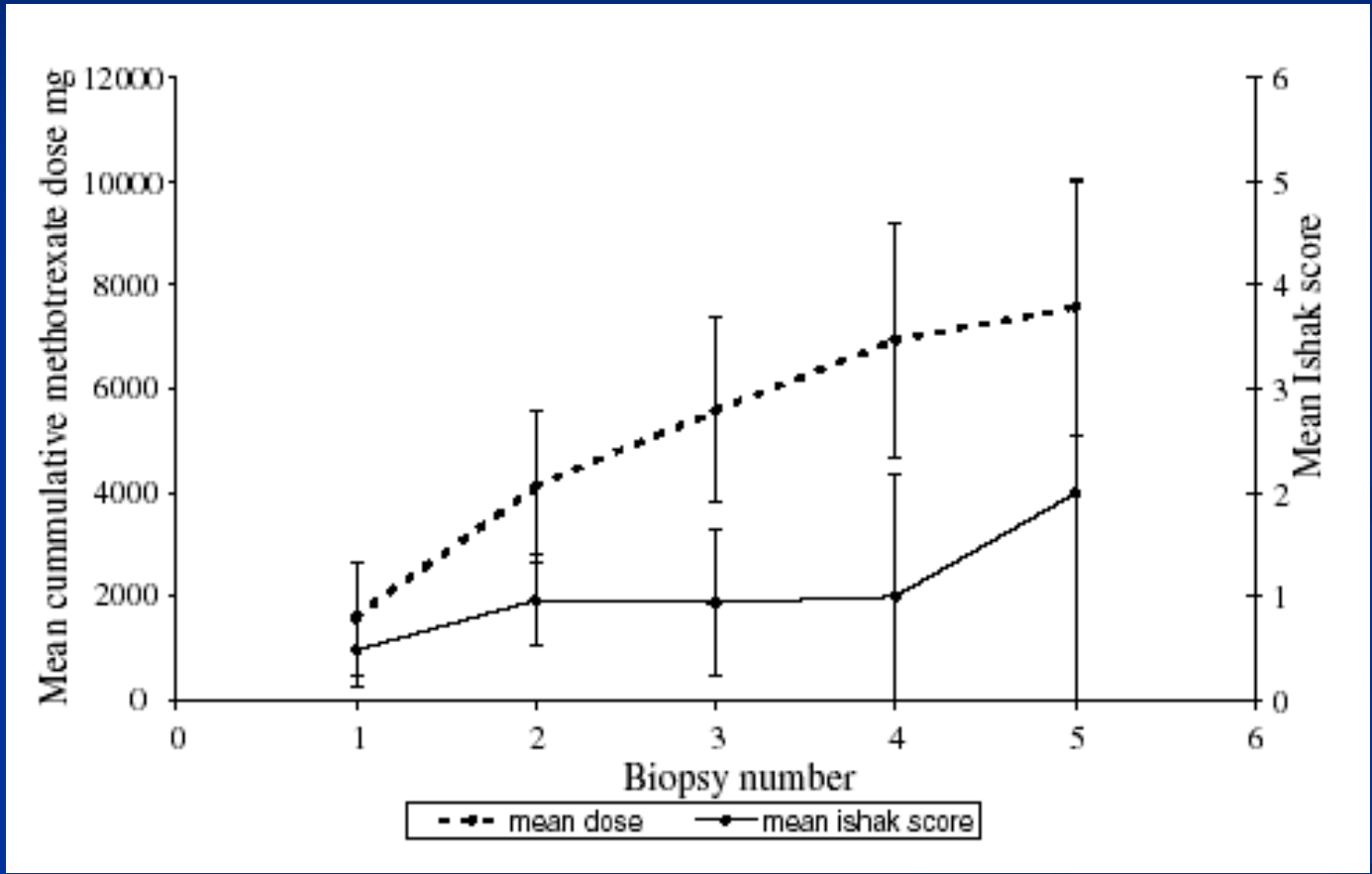
Methotrexate in psoriasis: guidelines for monitoring

A. Pre-methotrexate evaluation
1. Complete blood count
2. Renal function: serum creatinine, blood urea nitrogen, urine analysis and creatinine clearance
3. Liver chemistry: aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, albumin and hepatitis A, B and C serology test
4. Human immunodeficiency virus antibody determination in patients at risk of acquired immunodeficiency syndrome
B. Pre-treatment liver biopsy
If long-term methotrexate therapy is anticipated, initial liver biopsy should be performed (revision in 1998 suggested that the pre-treatment biopsy should be considered on the basis of the patient's relative risk)
C. Continuing laboratory studies
1. Complete blood count weekly for 2 weeks, then biweekly for 1 month and then monthly
2. Renal function studies: blood urea nitrogen and serum creatinine at 3–4-monthly intervals
3. Liver chemistry: aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin and albumin every 4–8 weeks (more frequent in the absence of initial liver biopsy)
D. Monitoring liver biopsy
A liver biopsy is recommended after a cumulative dose of about 1.5 g and thereafter at 1.0–1.5 g intervals
E. Interpretation of liver biopsy
Patients with grade 3a changes should have a repeat biopsy after 6 months
Patients with grade 3b or 4 changes should discontinue methotrexate, except in exceptional circumstances where follow-up biopsies should be performed

MTX Liver Injury

- Summary of guidelines (Roenigk 1972)
  - Pre-treatment biopsy for "high-risk" patients
  - Mandatory biopsy at cumulative dose of 1.5gm and 1gm intervals thereafter
  - Scoring is based on Roenigk classification (1-3 with regards to steatosis, nuclear pleomorphism, fibrosis, and portal inflammation)
    - Never been validated in other liver diseases
    - Does not correlate well with Scheuer or Ishak
  - Grade IIIA (mild fibrosis) may continue but need f/u bx in 6 months
  - Grade IIIB or higher discontinue therapy (mod fibrosis)

Relationship between the degree of fibrosis (Ishak score) and the cumulative methotrexate dose at the time of liver biopsy in 27 patients without advanced fibrosis prior to treatment.



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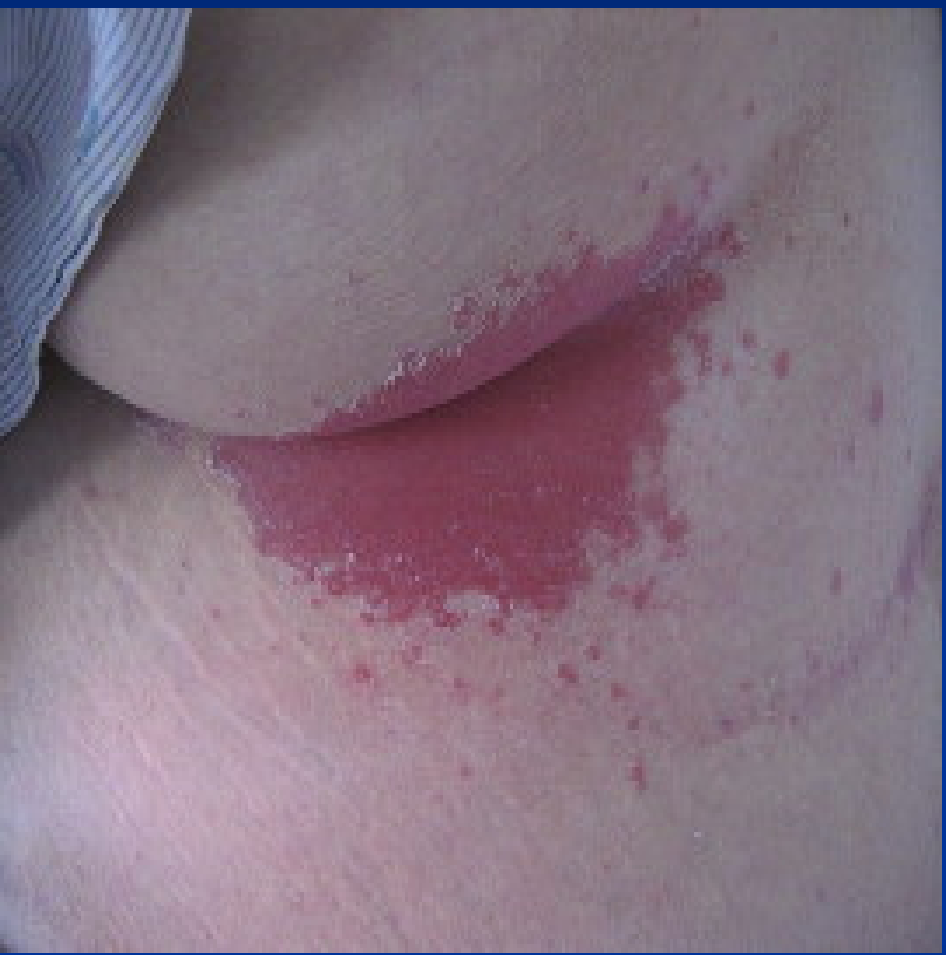
MTX Liver Injury

- Don't Biopsy
  - w/o risk factors
  - <20mg/wk (2.6%)
  - <4gm cumulative dose
  - w/o clinical indications
- Who's left?

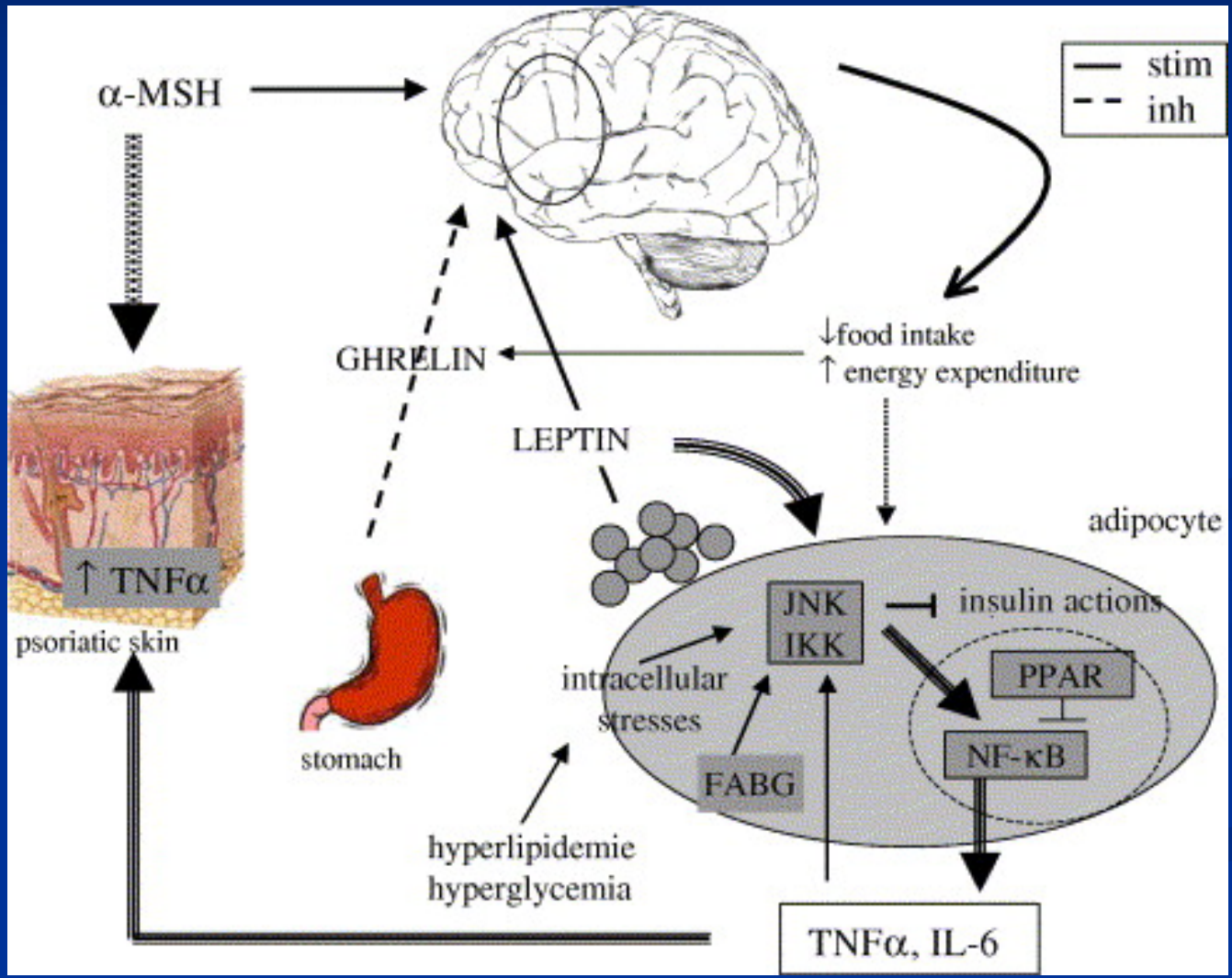
The Correlation Between Psoriasis and Metabolic Syndrome

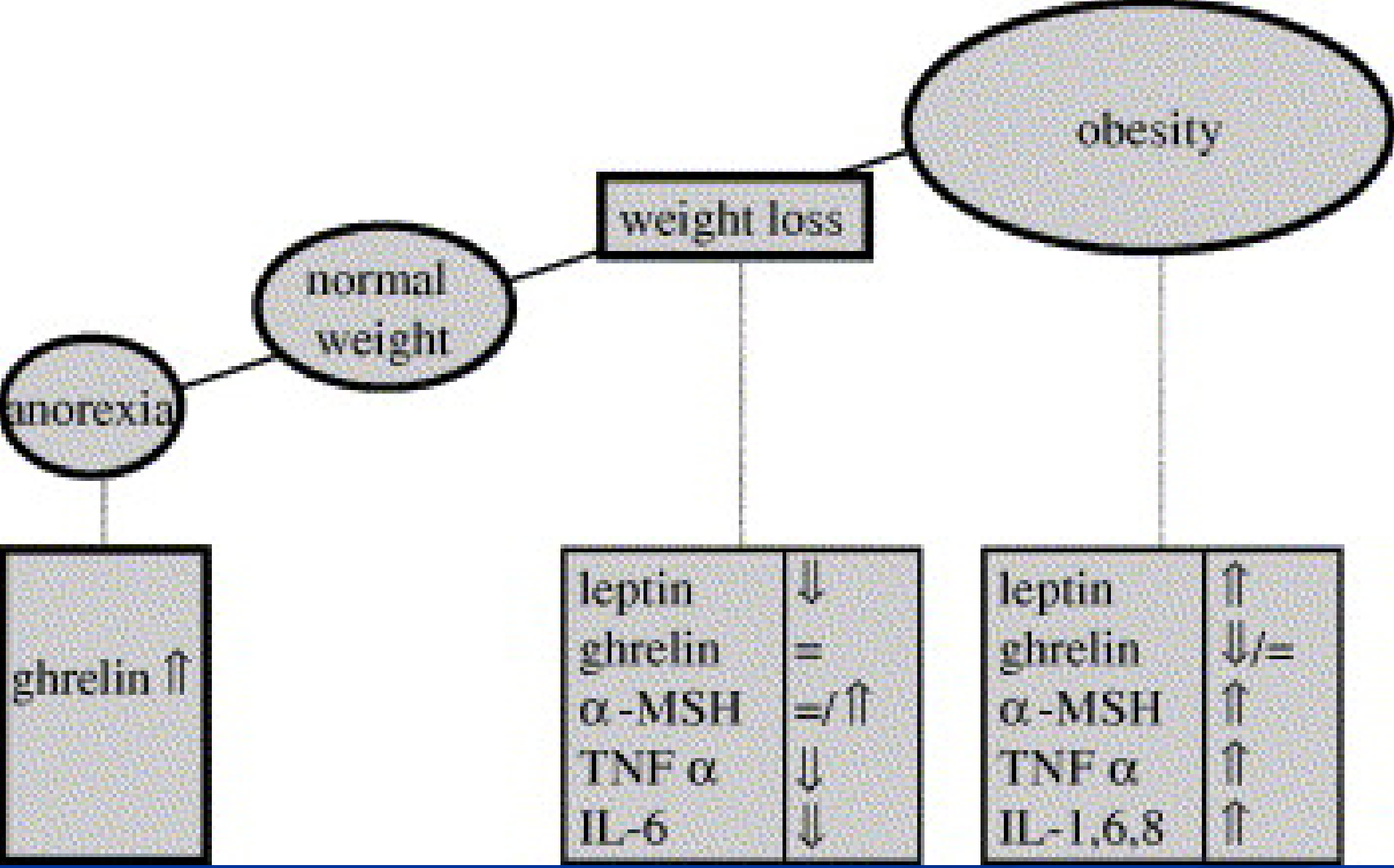


- Patients with obesity and diabetes have a higher prevalence of psoriasis (esp. inverse psoriasis).
- Incidence of psoriasis directly correlates with BMI
- The presence of the metabolic syndrome increases the severity of disease (i.e. they might need systemic treatment)

Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. J Am Acad Dermatol. 2007 Jun;56(6):901-16; quiz 917-20

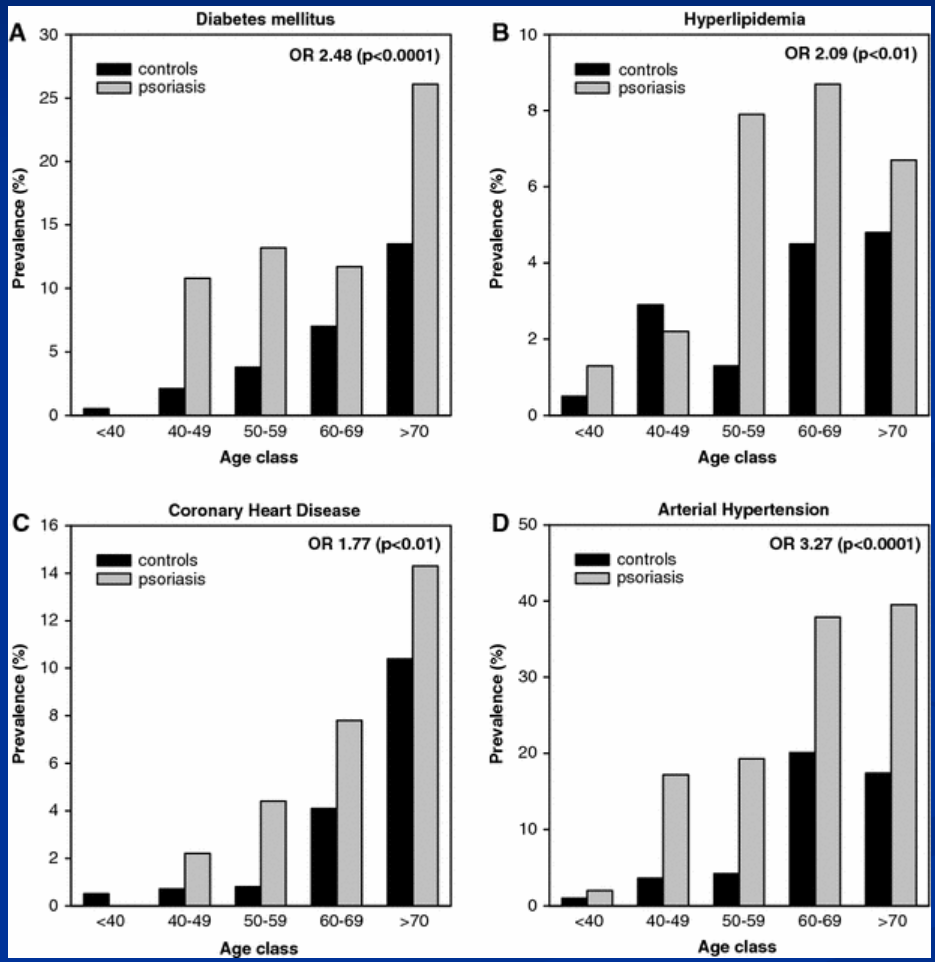
The Correlation Between Psoriasis and Metabolic Syndrome





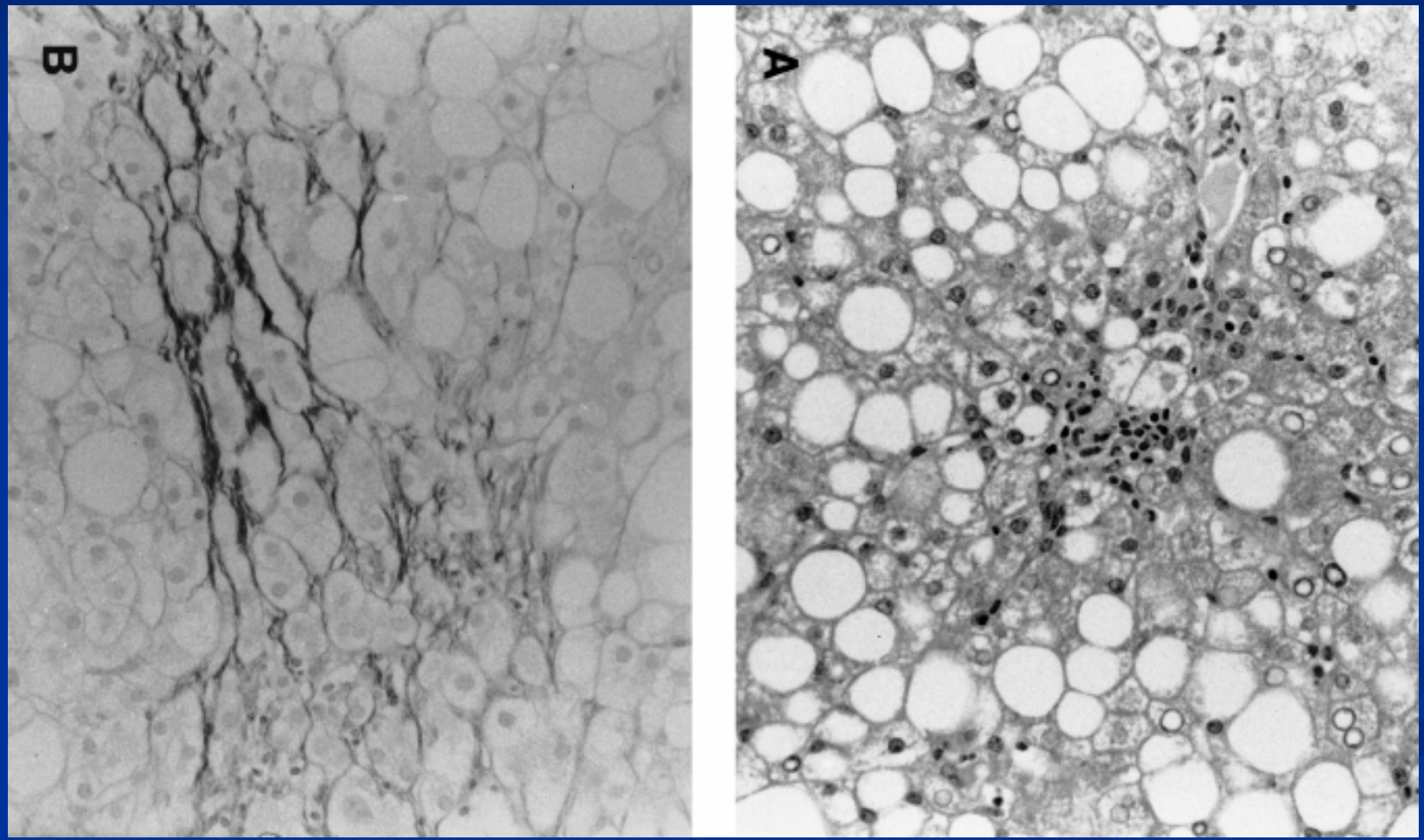
E.A. Hamminga, A.J. van der Lely, H. A.M. Neumann and H.B. Thio Chronic inflammation in psoriasis and obesity: Implications for therapy Medical Hypotheses Volume 67, Issue 4, 2006, Pages 768-773

Psoriatic Patients Have Systemic Disease!



Sommer et al. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis Archives of Dermatological Research Volume 298, Number 7 / December, 2007

Who's At Risk?



Psoriasis Patients

- Severe fibrosis and cirrhosis are relatively common (up to 17%).
- Studies of methotrexate hepatotoxicity in psoriasis patients have not rigorously controlled for other underlying chronic liver diseases including alcoholic liver disease, viral hepatitis and NASH.
- 20-80% of psoriatic patients have at least one component of metabolic syndrome.
- Dermatology guidelines developed in the 1980s recommend liver biopsy before therapy, after an initial total dose of 1.5 g of methotrexate, and every 1–1.5 g cumulative dose thereafter.
- Finding moderate-to-severe fibrosis or cirrhosis would preclude further therapy

M. S. Campbell, K. R. Reddy (2004) The evolving role of liver biopsy . Alimentary Pharmacology & Therapeutics 20 (3), 249–259.

Rheumatoid Arthritis Patients

- The prevalence of significant fibrosis and cirrhosis is rare.
  - More rigorous exclusion of patients with underlying liver disease
  - Patients with psoriasis often have risk factors in common with NAFLD (e.g obesity, dm). RA pt's don't.
- Rheumatology guidelines recommend pre-treatment liver biopsy if chronic liver disease is suspected.
- Liver biopsy during therapy is recommended if a majority (5/9) of ASTs over a year's time (repeated every 4–8 weeks) is elevated or if serum albumin is decreased.

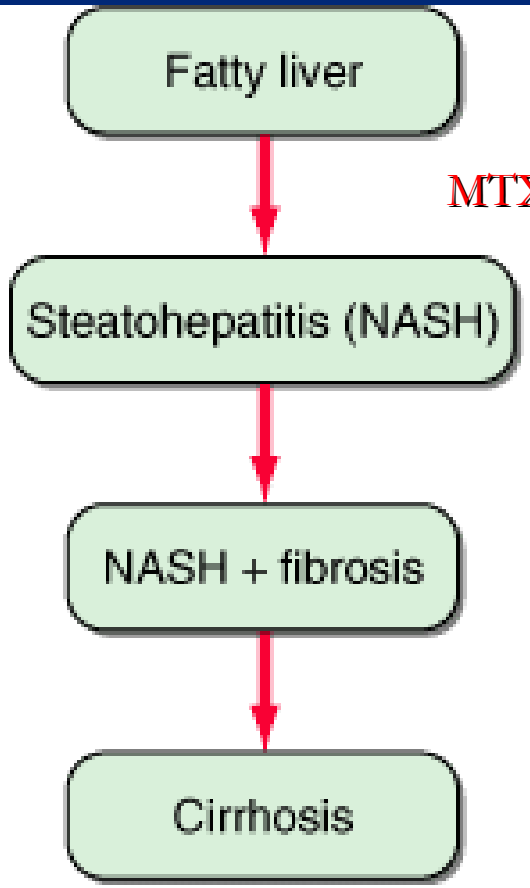
M. S. Campbell, K. R. Reddy (2004) The evolving role of liver biopsy . Alimentary Pharmacology & Therapeutics 20 (3), 249–259.

Who's At Risk of MTX Injury?

- The risk factors for MTX induced liver injury = Risk factors for NASH
- Well established risk factors include:
  - DM
  - EtOH use
  - Obesity
- Pre-existing NASH, possibly aggravated by MTX, may be the main cause of the liver damage
- Two-Hit Phenomenon with MTX-induced Folate deficiency or increased gut permeability representing the second hit.
- Long-term MTX therapy causes a liver injury that resembles NASH

Rosenberg et al. **Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment** **Journal of Hepatology** Volume 46, Issue 6, June 2007, Pages 1111-1118

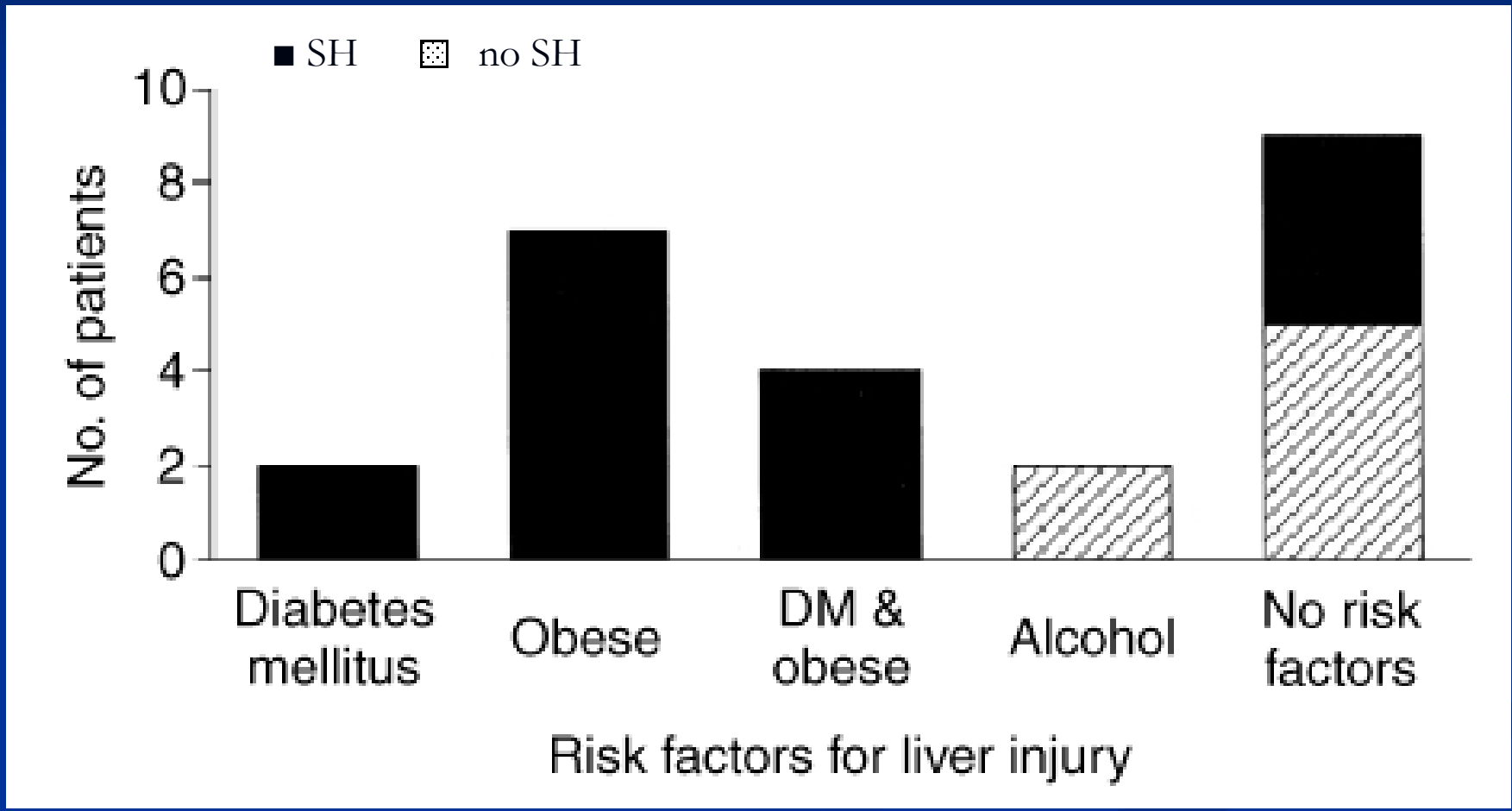
MTX/Folate deficiency: A Second Hit?



MTX induced Folic acid deficiency
Increased gut permeability

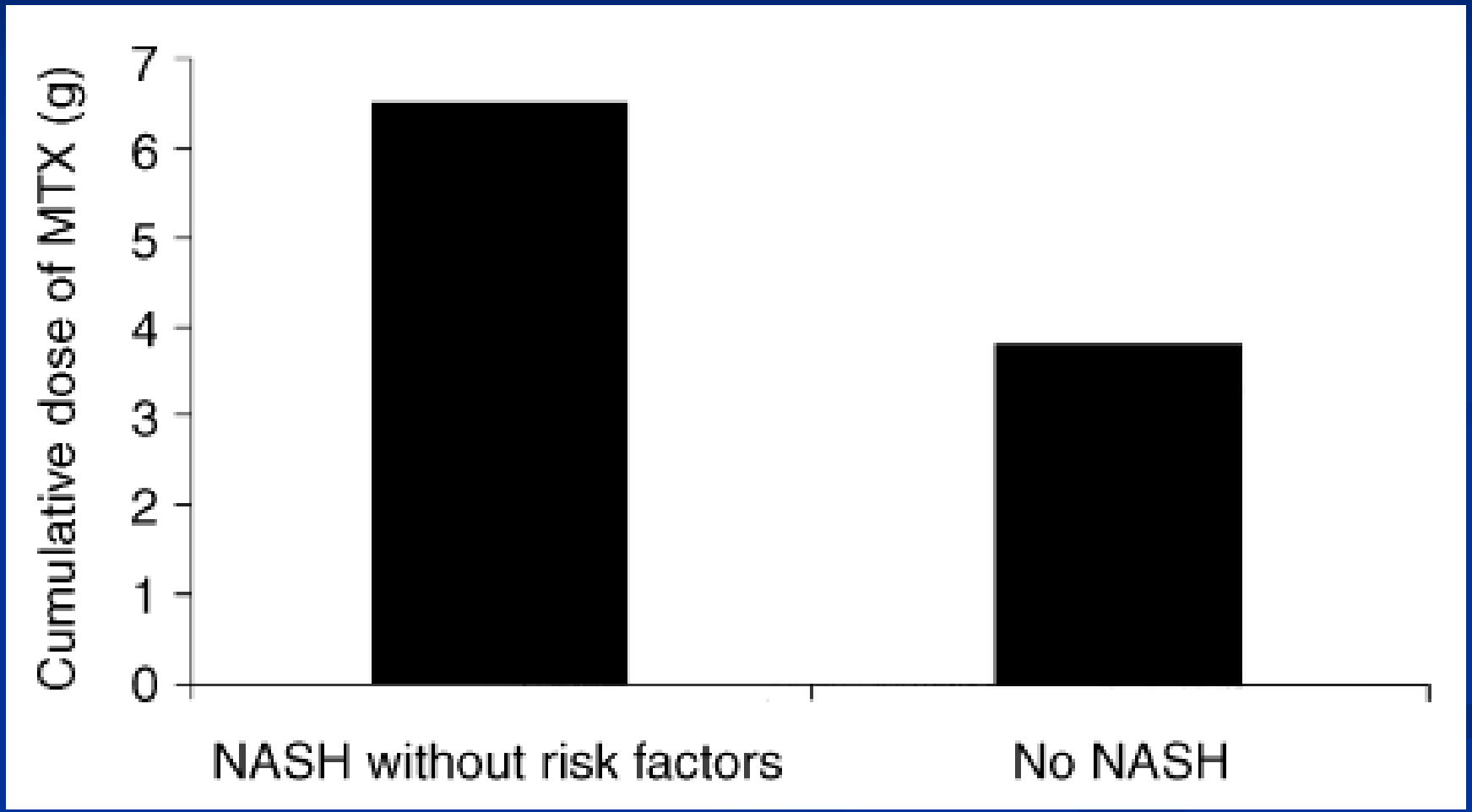
Source: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Isselbacher KJ: *Harrison's Principles of Internal Medicine*, 16th Edition: http://www.accessmedicine.com

Who's At Risk?



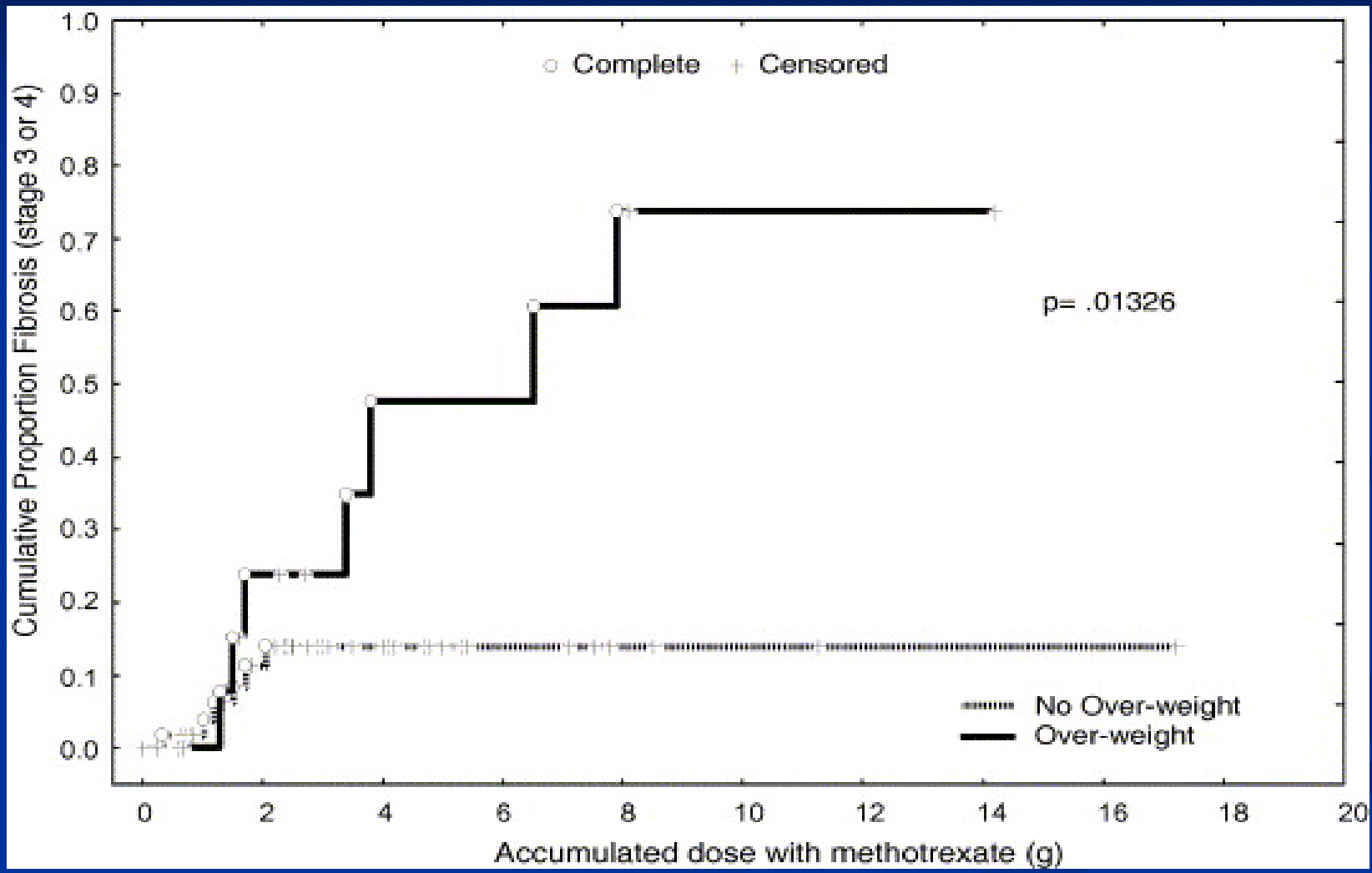
Gerald Langman, Pauline De La M Hall, Gail Todd (2001)Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. Journal of Gastroenterology and Hepatology 16 (12), 1395–1401.

Who's At Risk?



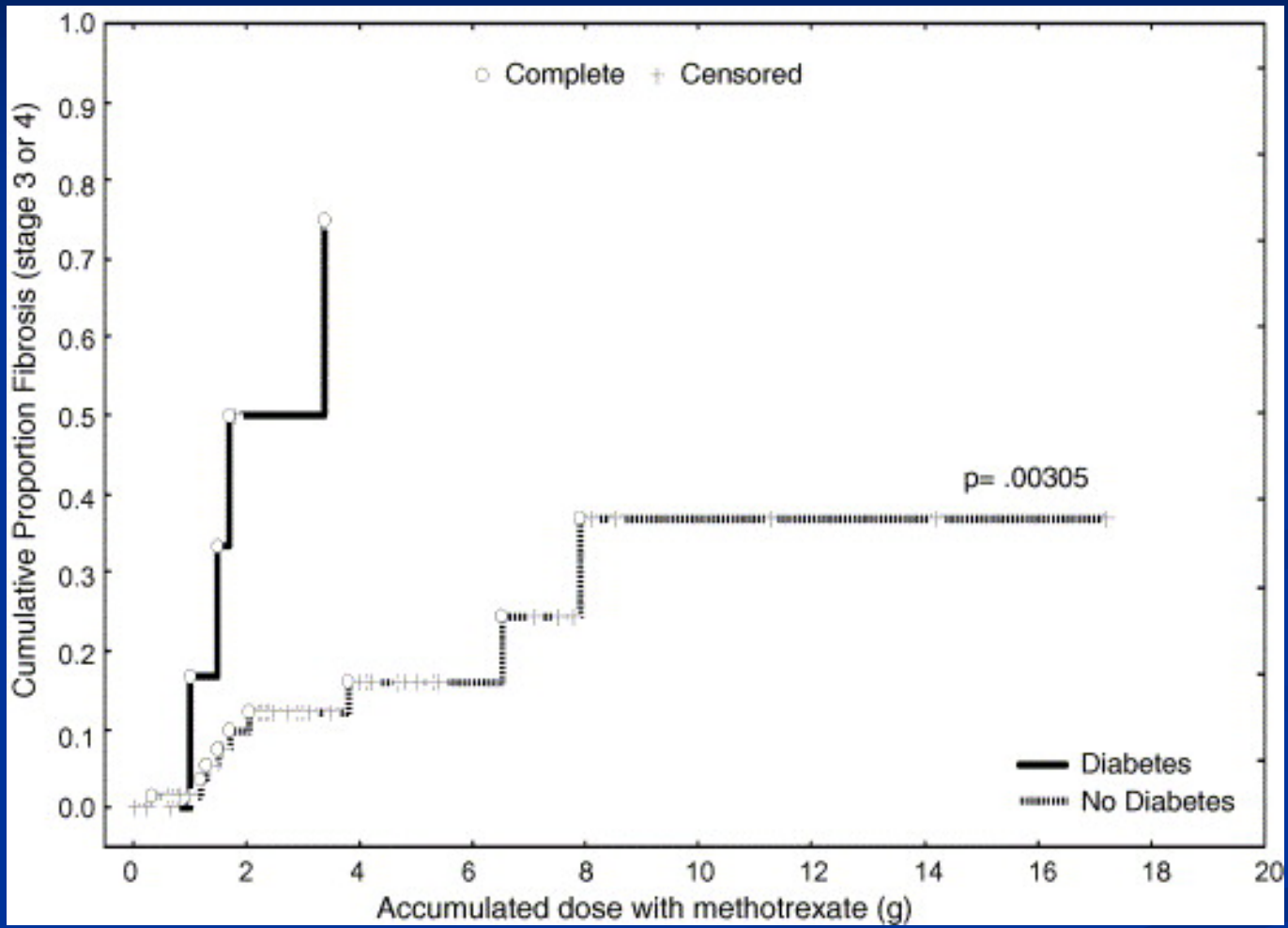
Gerald Langman, Pauline De La M Hall, Gail Todd (2001)Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. Journal of Gastroenterology and Hepatology 16 (12), 1395–1401.

Obesity + MTX



Rosenberg et al. **Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment** Journal of Hepatology Volume 46, Issue 6, June 2007, Pages 1111-1118

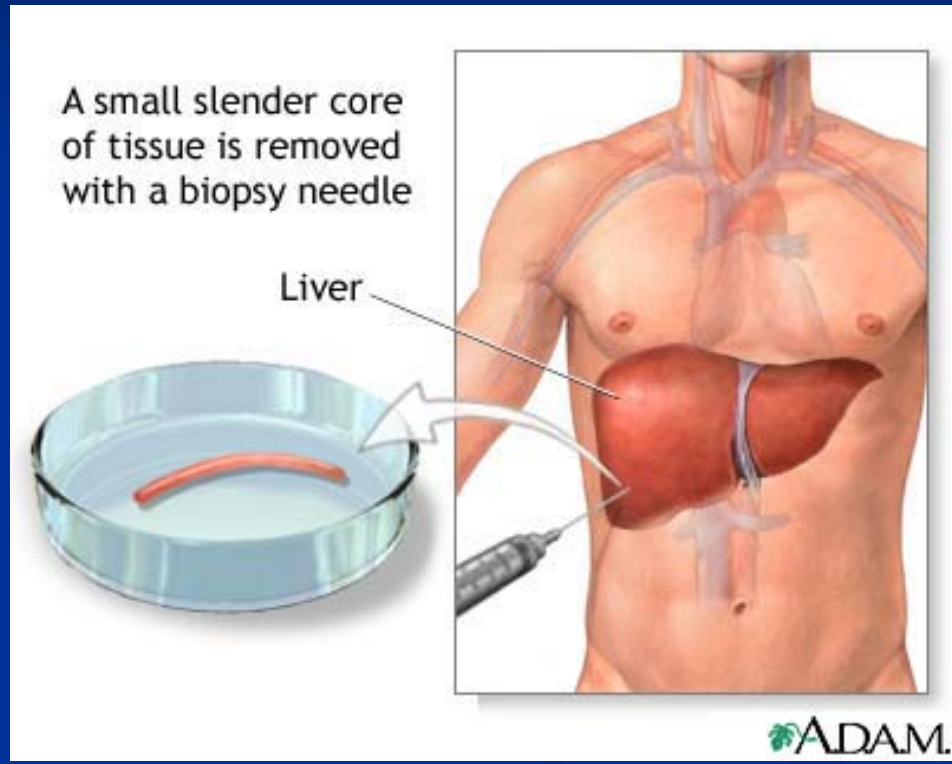
Diabetes and MTX



Rosenberg et al. **Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment** Journal of Hepatology Volume 46, Issue 6, June 2007, Pages 1111-1118

Noninvasive Measures of Fibrosis

- What's the big deal?
  - Mort: 1:1000-1:10,000
  - Morb: 1:100
  - 1/50,000th
  - 30% Sampling error
  - $2200
  - Time
  - Avoid needles



Comparison of Liver Biopsy and Blood Tests for Evaluation of Fibrosis

	Liver Biopsy	Blood Tests
Good	Direct; semi-quantitative	Potentially a measure of global fibrosis; suitable for serial observation
Bad	Sampling error; use for serial observation limited by risk and patient acceptance	Indirect; not shown to be useful for tracking a change in fibrosis status; known false +
Risks	Pain in 10%, 15%; significant bleeding in 0.2%	None
Cost	Expensive	Varies; the cost of proprietary tests is similar to that of biopsy

Rocky DC and Bissell DM. Noninvasive measures of liver fibrosis. Hepatology. 2006 Feb;43(2 Suppl 1):S113-20

Features of an Ideal Marker of Liver Fibrosis

1. Liver specific.
2. Levels not influenced by alterations in liver, renal, or reticuloendothelial function.
3. Measurement of one or more of the following processes:
    1. Stage of fibrosis
    2. Activity of matrix deposition
    3. Activity of matrix removal
4. Easy to perform.

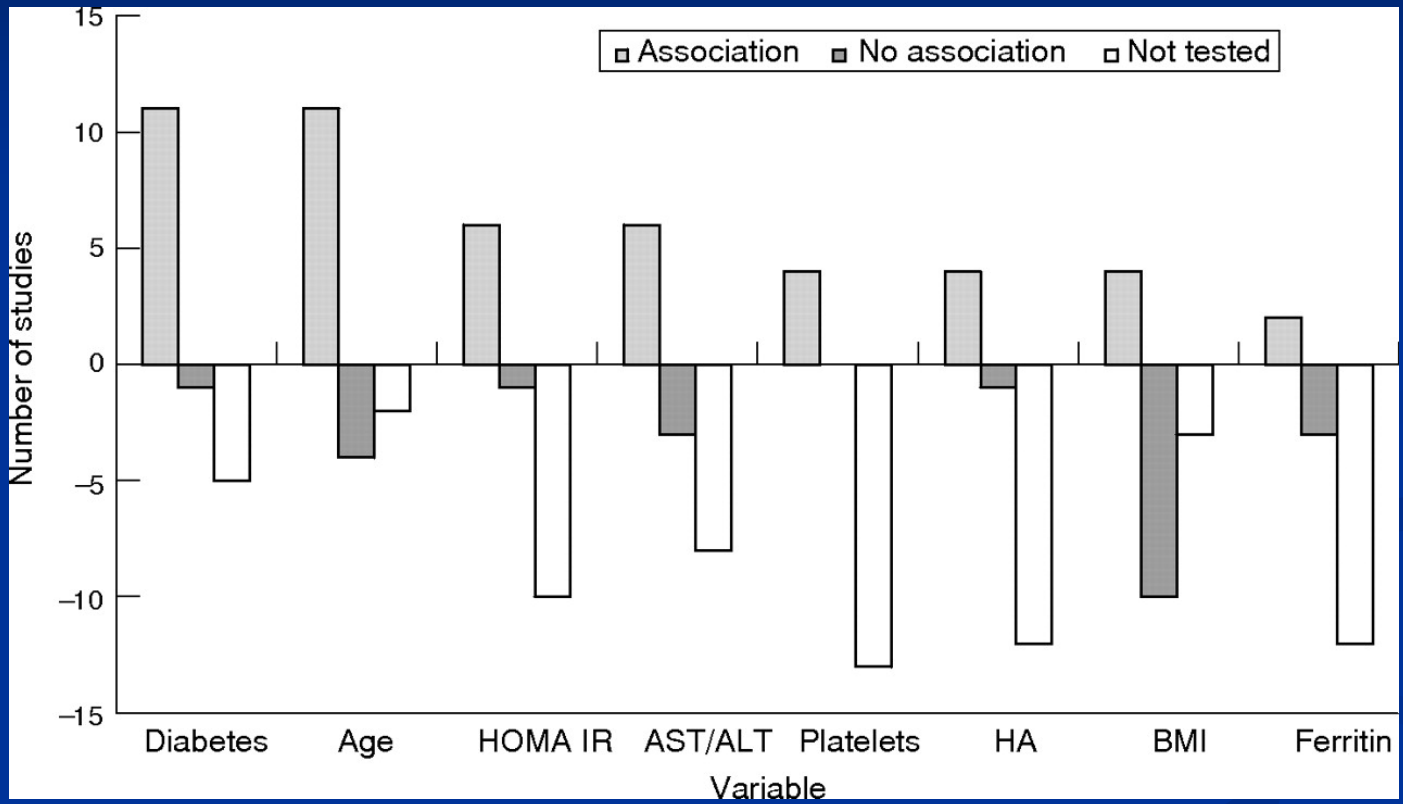
Afdhal, Nezam H. & Nunes, David
Evaluation of Liver Fibrosis: A Concise Review.
American Journal of Gastroenterology **99** (6), 1160-1174.

Variables associated with fibrosis

Category	Variable
Sociodemographic and anthropometric	Age, sex, BMI, WHR
Simple liver biochemistry and haematology	ALT, AST, AST/ALT ratio, platelets, bilirubin, ferritin, transferrin saturation, albumin.
Features of metabolic syndrome or glucose sensitivity	Diabetes, hypertension, HOMA-IR, OGIS, metabolic syndrome, raised triglycerides, QUICKI, adiponectin, leptin, hyperlipidaemia
Fibrosis markers	HA, TIMP 1, laminin, type IV collagen, PIIINP
Miscellaneous	Malondialdehyde, C peptide, polymorphisms of transforming growth factor and angiotensinogen, IgA, glutathione, arachidonic acid, oxidised cardiolipin, coenzyme Q, and copper oxide dismutase

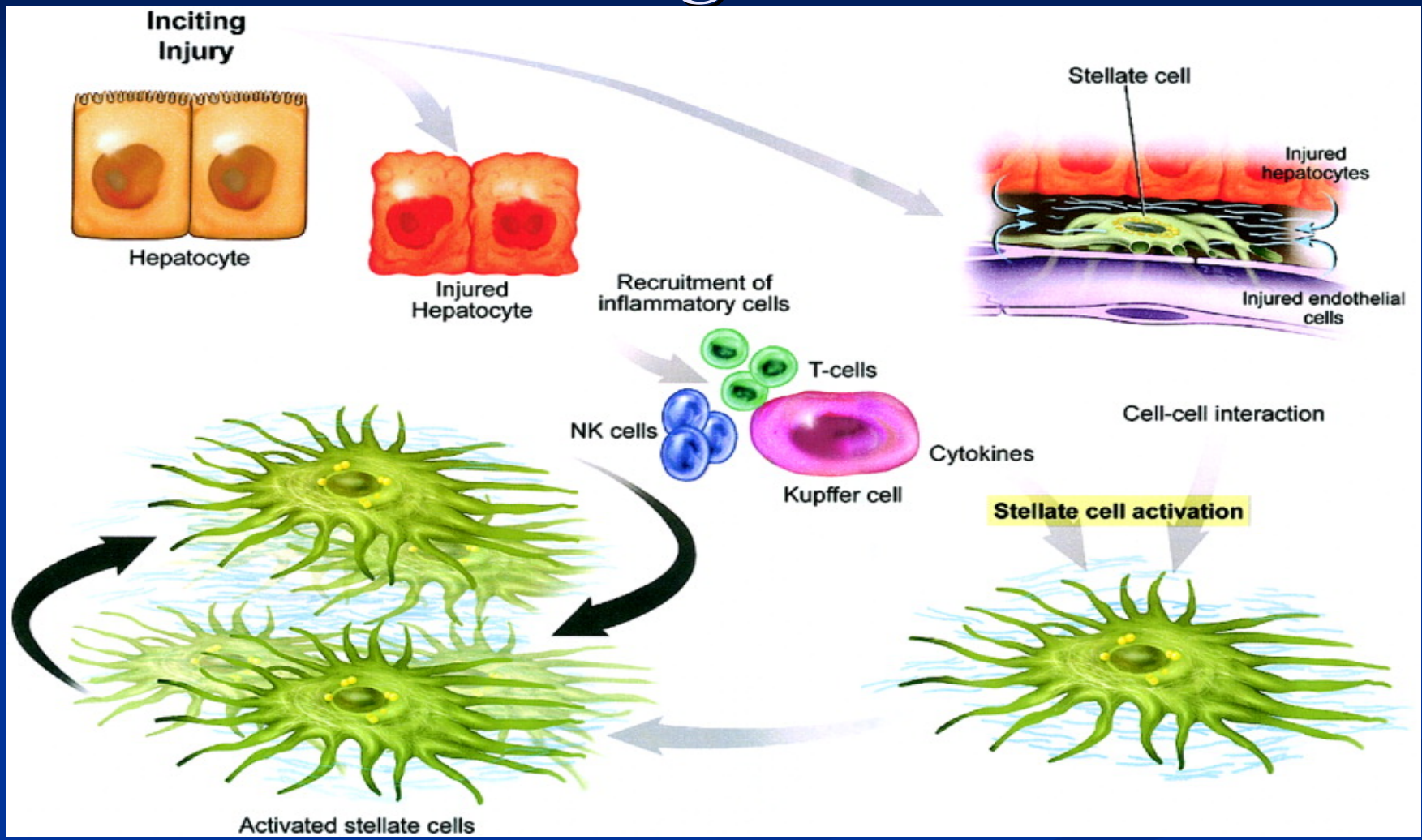
Gut 2006;**55**:1650-1660

Variables associated with severe fibrosis. HOMA-IR, homeostatic insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HA, hyaluronic acid; BMI, body mass index.



Guha, I N et al. Gut 2006;55:1650-1660

Pathogenesis



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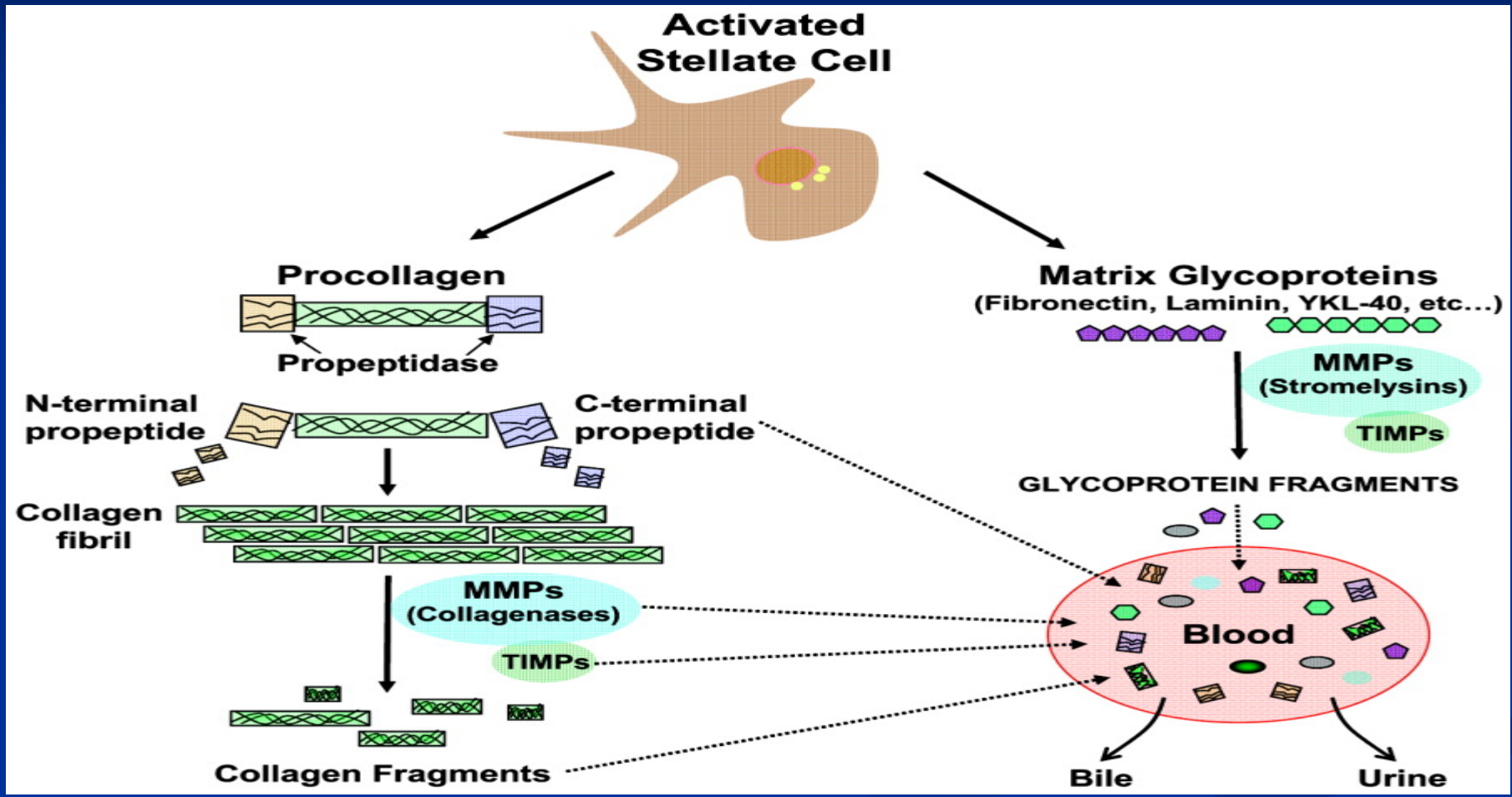


Rocky DC and Bissell DM. Noninvasive measures of liver fibrosis. Hepatology. 2006 Feb;43(2 Suppl 1):S113-20

Markers of Matrix Turnover and Relationship to ECM Deposition and Removal

- Markers of matrix deposition
  - Procollagen I C terminal
  - Procollagen III N terminal
  - Tenascin
  - Tissue inhibitor of metalloproteinase TIMP
  - TGF-β
- Markers of matrix removal
  - Procollagen IV C peptide
  - Procollagen IV N peptide (7-S collagen)
  - Collagen IV
  - Undulin
  - Metalloproteinase MMP
  - Urinary desmosine and hydroxylysylpyridinoline
- Uncertain
  - Hyaluronan
  - Laminin
  - YKL-40 (Chondrex)

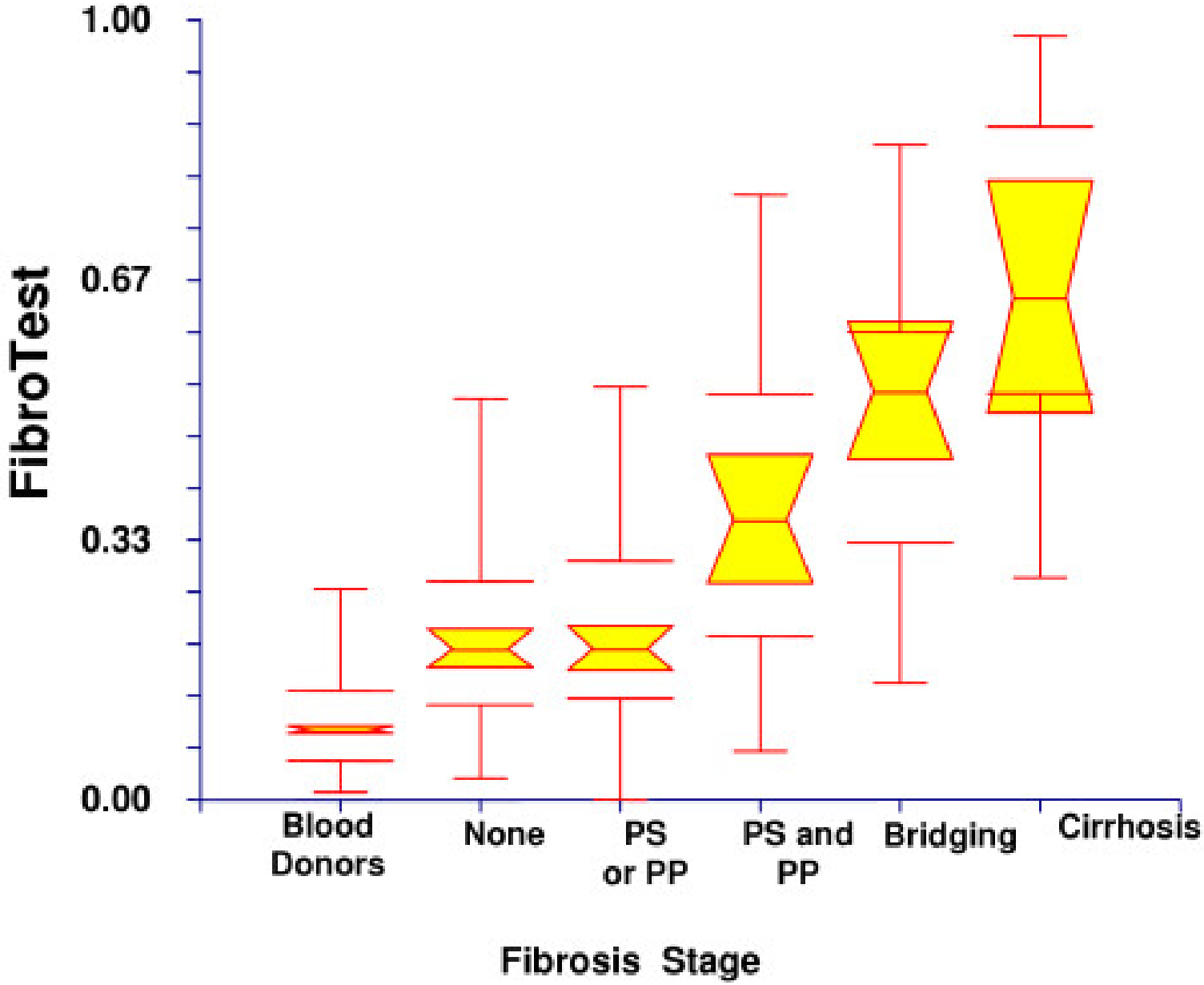
Afdhal NH and Nunes D.

Routine Lab/Propriety Test Panels

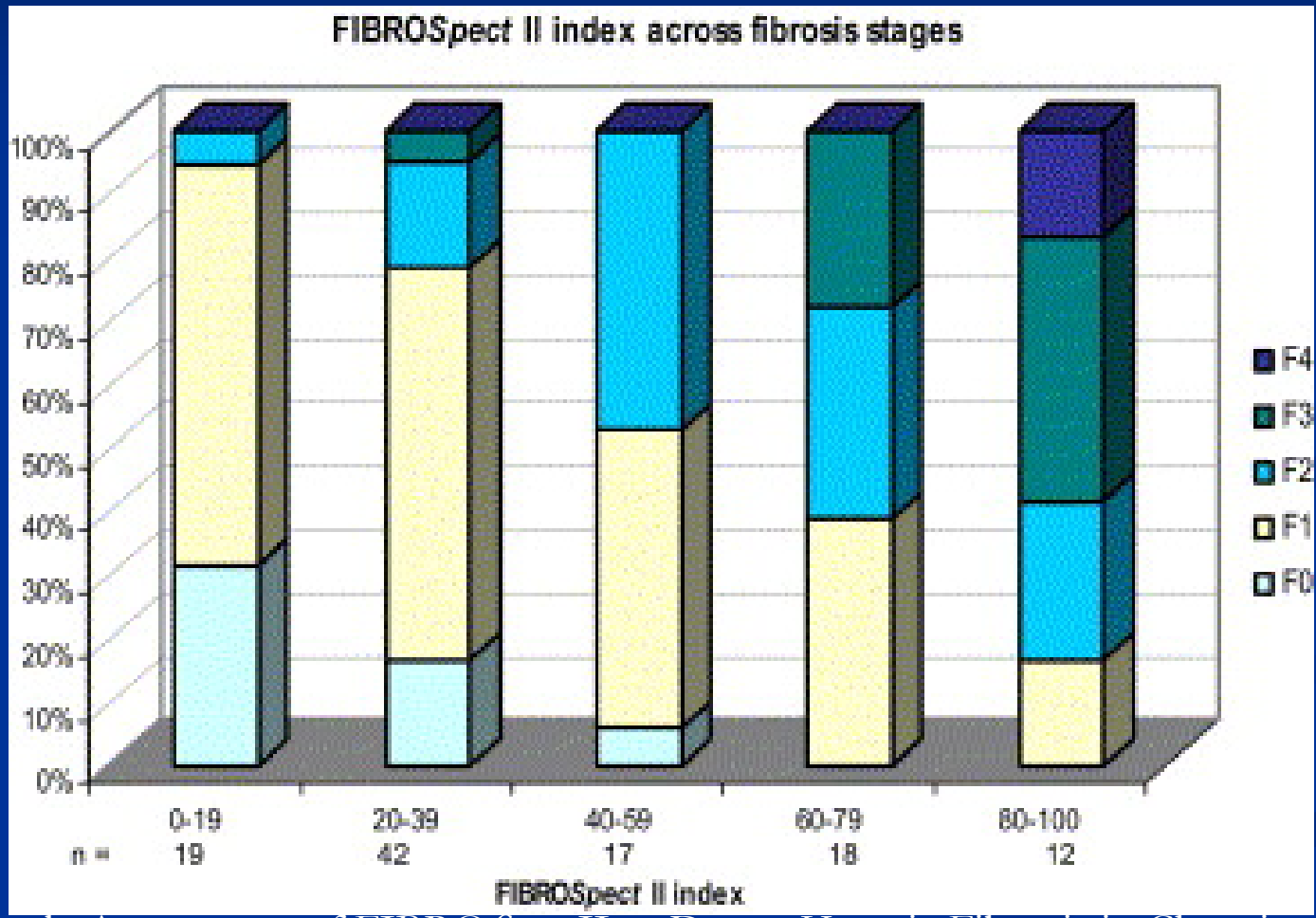
- AST/ALT > 1
- AST/ Platelet Count (APRI)
- PGA index: Prothrombin time, GGT, apolipoprotein A1
- PGAA index: Prothrombin time, GGT, apolipoprotein A1, and alpha-2-macroglobulin
- Fibrotest: Alpha-2 macroglobulin, GGT, Haptoglobin, Apolipoprotein A1, Total bilirubin
- Fibrospect: Hyaluronic acid, TIMP-1, alpha-2-macroglobulin

Fibrotest

- Components
  - Alpha-2 macroglobulin
  - Haptoglobin
  - GGT
  - Apolipoprotein A1
  - Total bilirubin
- Markers of fibrogenesis, not fibrosis
- Validated in several cohorts
  - Good for detecting fibrosis
- False + due to ↑ bili, ↓ hapto, Gilbert's, cholestasis, & acute inflammation


1.00
0.67
0.33
0.00
FibroTest
Blood Donors
None
PS or PP
PS and PP
Bridging
Cirrhosis
Fibrosis Stage

Fibrospect



Zaman et al., Assessment of FIBRO*Spect* II to Detect Hepatic Fibrosis in Chronic Hepatitis C Patients **The American Journal of Medicine**. Volume 120, Issue 3, March 2007, Pages 280.e9-280.e14

Serum markers for detecting any stage of fibrosis in NAFLD

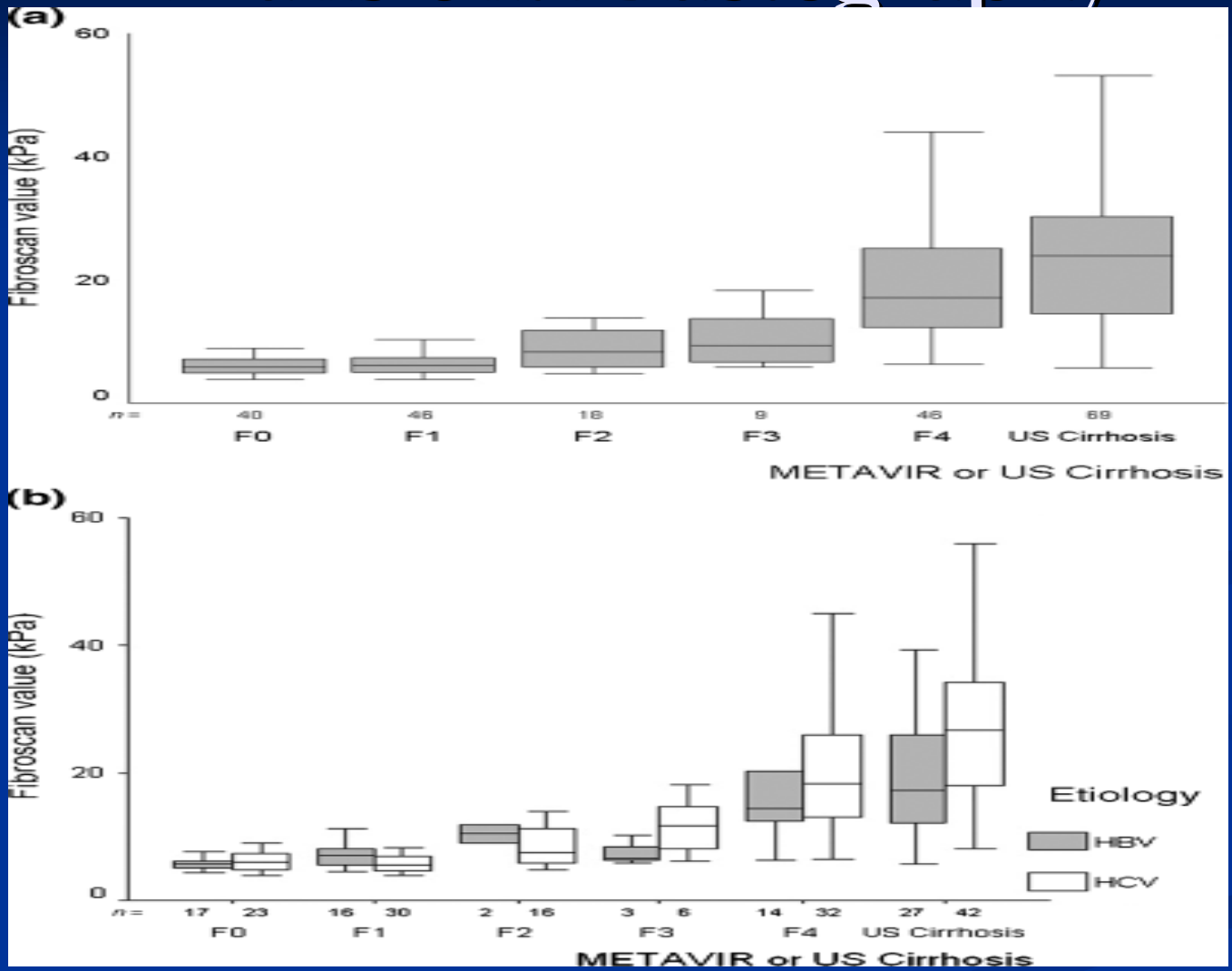
Serum marker	Sensitivity (%)	Specificity (%)	Reference
Laminin	82	89	dos Santos et al.
Type IV collagen 7S	70	81	Sakugawa et al.
Collagen IV	64	89	dos Santos et al.
ELF Score (Age, HA, PIIINP, TIMP1)	89	96	Rosenberg et al.
FibroSure (α2-macroglobulin, apolipoproteinA1, haptoglobin, total bilirubin, and γ-glutamyltranspeptidase)	77	77	Poynard et al.

Luca Miele[a], Alessandra Forgione[a], Giovanni Gasbarrini[a] and Antonio Grieco. **Translational Research** Volume 149, Issue 3, March 2007, Pages 114-125 Noninvasive assessment of fibrosis in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Radiography

- U/S, CT, MRI (90% sens): Don't distinguish fatty infiltration from inflammation. No disease vs. mild/mod disease vs. advanced disease only
- Transient Elastography
  - Increased stiffness
  - Proven (sens 64%/spec 88%) good for ruling out
  - When used in combination with Fibrotest predictive value with an AUROC was 0.88
  - Limited use in obese patients or those with ascites
  - Has not been shown to distinguish fibrosis from steatosis
- MRS estimates cell membrane turnover and fibrosis

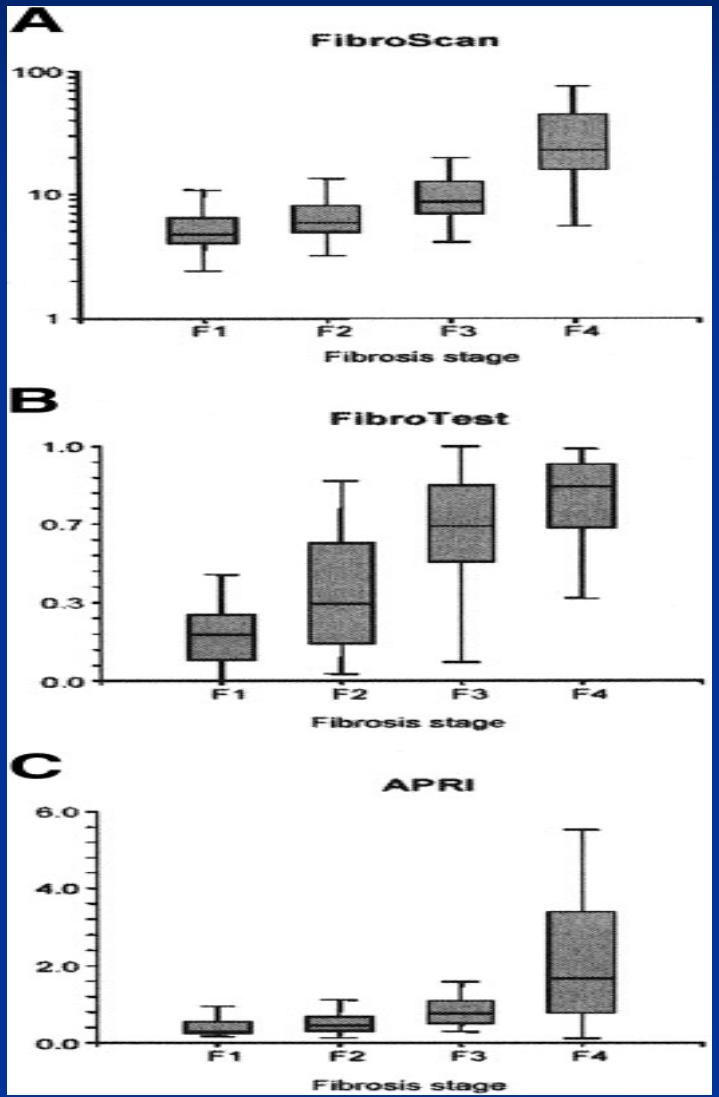
Transient Elastography

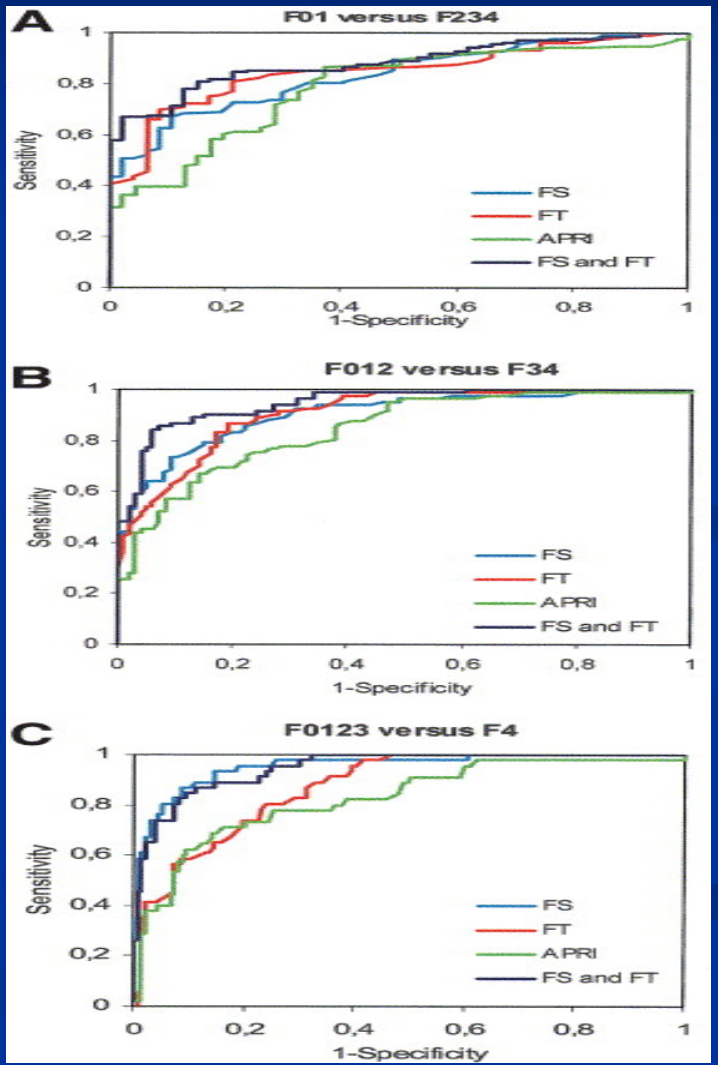


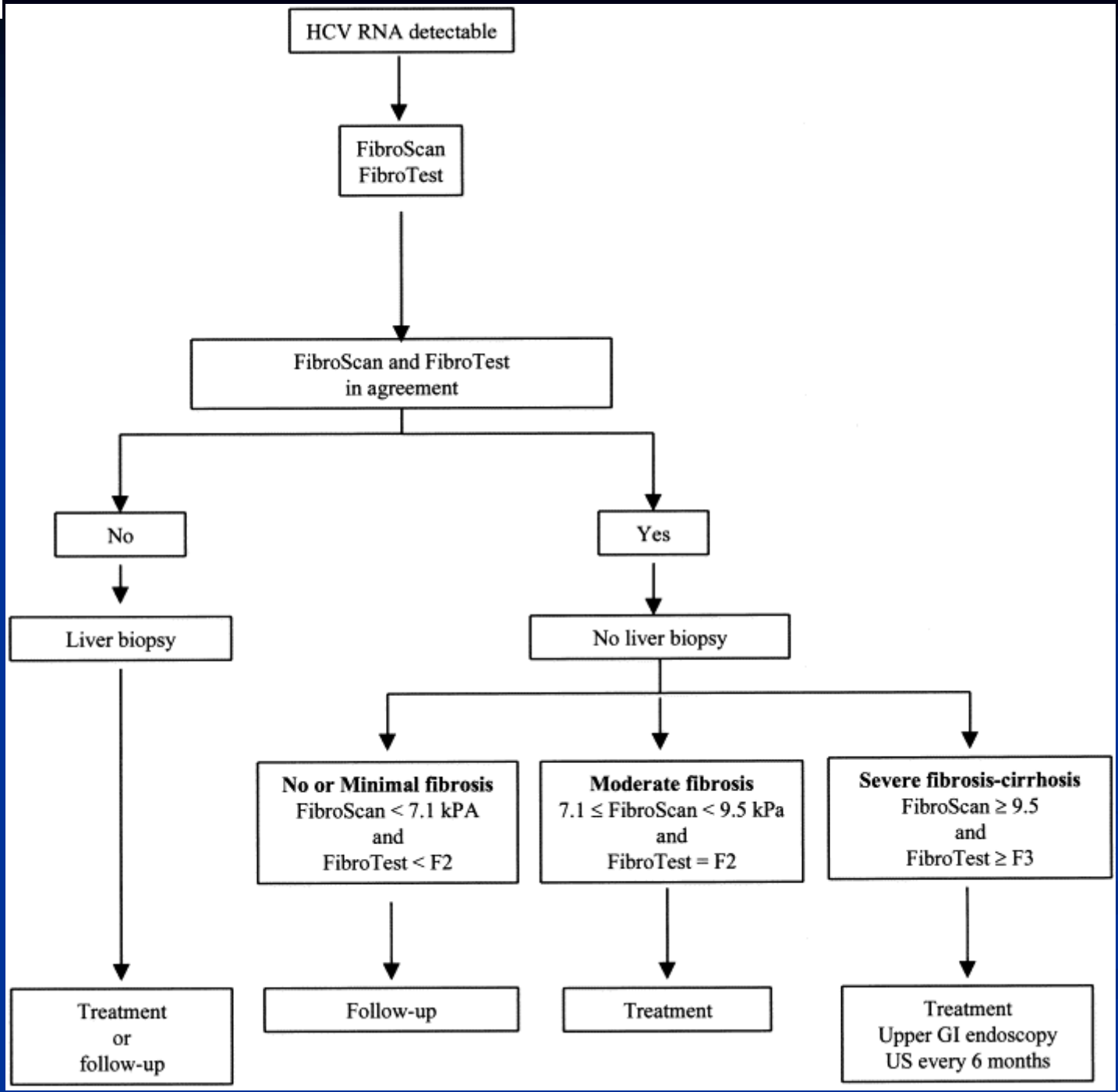
Coco, B., Oliveri, F., Maina, A. M., Ciccorossi, P., Sacco, R., Colombatto, P., Bonino, F. & Brunetto, M. R. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *Journal of Viral Hepatitis* **14** (5), 360-369.

Castéra et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C.

Gastroenterology **Volume 128, Issue 2**, February 2005, Pages 343-350

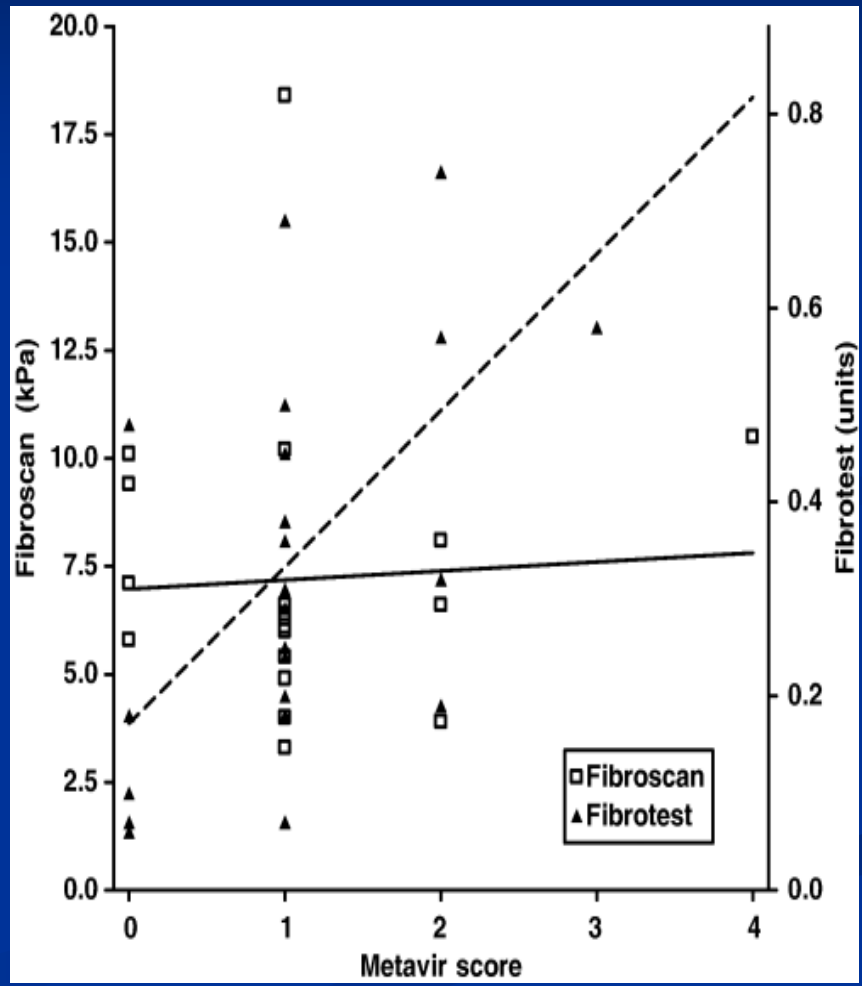





HCV RNA detectable
FibroScan
FibroTest
FibroScan and FibroTest
in agreement
No
Yes
Liver biopsy
No liver biopsy
No or Minimal fibrosis
FibroScan < 7.1 kPA
and
FibroTest < F2
Moderate fibrosis
7.1 ≤ FibroScan < 9.5 kPa
and
FibroTest = F2
Severe fibrosis-cirrhosis
FibroScan ≥ 9.5
and
FibroTest ≥ F3
Treatment
or
follow-up
Follow-up
Treatment
Treatment
Upper GI endoscopy
US every 6 months

NONINVASIVE MARKERS FOR MTX INDUCED LIVER INJURY

- 24 psoriasis patients who had a recent liver biopsy during MTX use.
- Fibroscan((R)) and Fibrotest were compared with liver histology.
- Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver fibrosis.



Berends, et al. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan® predicts the absence of significant liver fibrosis. *Liver International* **27** (5), 639-645.

Methotrexate (MTX) induced liver injury

	Fibrotest ≥F2	Fibroscan ≥F2
Optimal cut-off	0.31	7.1 kPa
Sensitivity (%)	83	50
Specificity (%)	61	88
Accuracy (%)	67	70
Positive predictive value (%)	42	33
Negative predictive value (%)	92	86

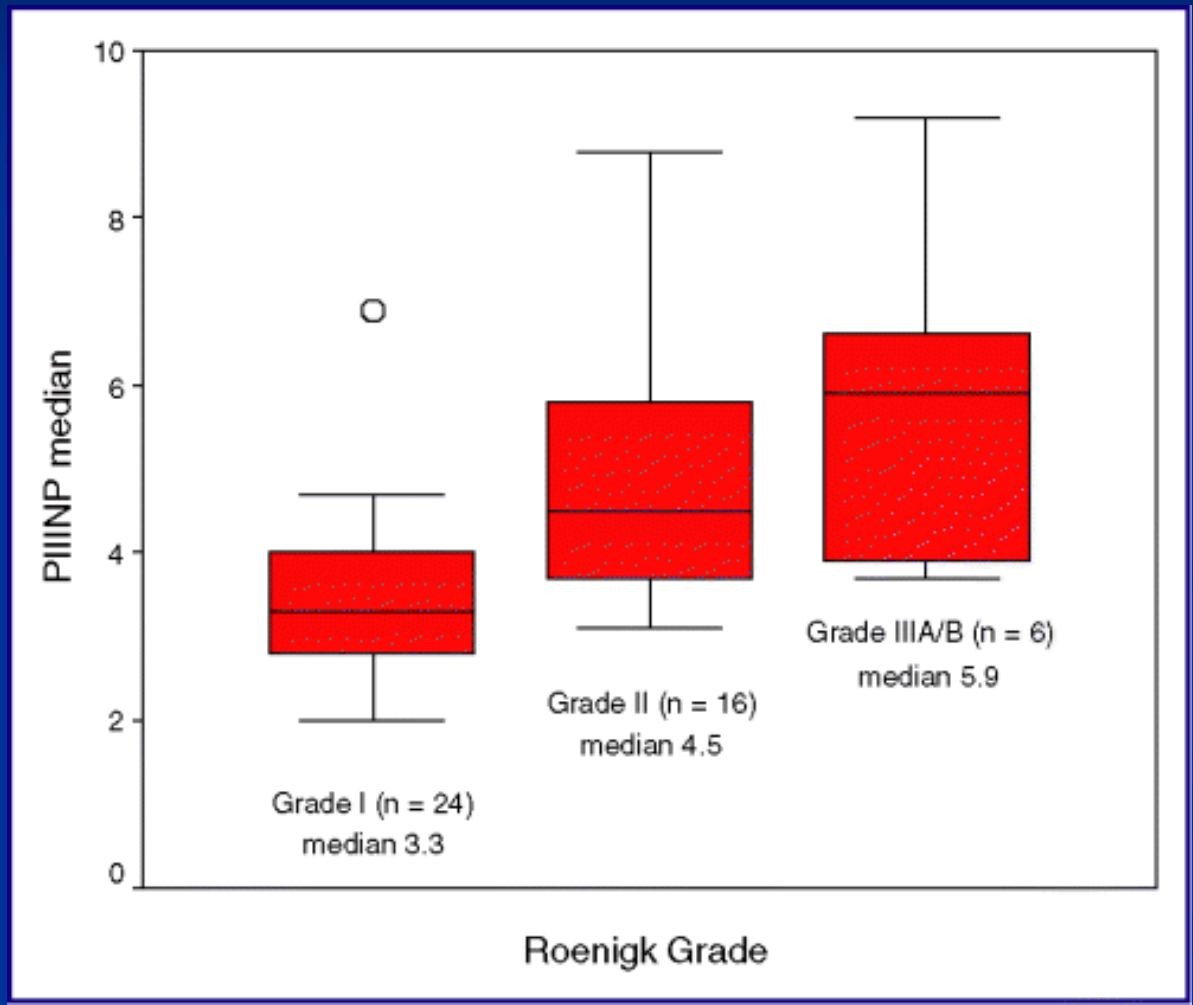
Berends, et al. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan® predicts the absence of significant liver fibrosis. *Liver International* **27** (5), 639-645.

Aminoterminal peptide of type III procollagen (PIIINP)

- 34 patients, 46 liver biopsies compared with the results of contemporaneous PIIINP assays.
- No biopsies showing fibrosis where all associated PIIINP assays were normal.
- All four biopsy pairs defined as showing deterioration had abnormal results on over half of the intervening PIIINP assays.
- There were no biopsy pairs showing deterioration where all intervening assay results were normal.
- However, 63% of stable biopsy pairs had at least one abnormal intervening assay.
- Would have reduced the number of biopsies by 45%
- Conclusion: follow-up liver biopsies, as recommended by published guidelines, for patients on long-term low-dose methotrexate can be avoided if PIIINP levels are consistently normal.

Maurice et al., Br J Dermatol. 2005 Mar;152(3):451-8.

Aminoterminal peptide of type III procollagen (PIIINP)



Maurice et al., Br J Dermatol. 2005 Mar;152(3):451-8.

Aminoterminal peptide of type III procollagen (PIIINP)

Proportion of PIIINP assays > 4·2 µg L^{-1}	Roenigk grade			Total
	I	II	IIIA/B	
None	15	5	0	20
< 50%	4	2	2	8
≥ 50%	5	2	1	8
All	0	7	3	10
Total	24	16	6	46

Maurice et al., Br J Dermatol. 2005 Mar;152(3):451-8.

MTX Liver Injury

- Don't Biopsy
  - w/o risk factors
  - <20mg/wk (2.6%)
  - <4gm cumulative dose
  - w/o clinical indications
  - those with normal PIIINP
- From my perspective
  - Don't use mtx in patients with metabolic syndrome
  - Use anti-TNF alpha therapy
- Who's left?
  - Combined elastography and propriety tests
  - Genetics

Future Directions

- What happened to patients on methotrexate and embrel?
- Would probiotics be protective in MTX liver injury?