

Current management of NASH

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- Brazil

Disclosures

Partner of HEPATOSCAN Medical Services® -

Commercial interest in transient liver elastography using FibroScan[®].

- Most common liver disease in western countries
- Hepatic manifestation of metabolic syndrome (MetS)
 - ✓ World prevalence: 6-46%
 - ✓ Obesity III: 90%
 - ✓ USA: 10-46%; NASH: 3-5%
 - ✓ Brazil: 19-35%

Vernon, et al. Aliment Pharmacol Ther 2011 Williams, et al. Gastroenterology 2011 Lazo, et al. Am J Epidemiol 2013 Parise, et al. 2003 Xarnikowski, et al. 2007

• Major factors related to NAFLD:

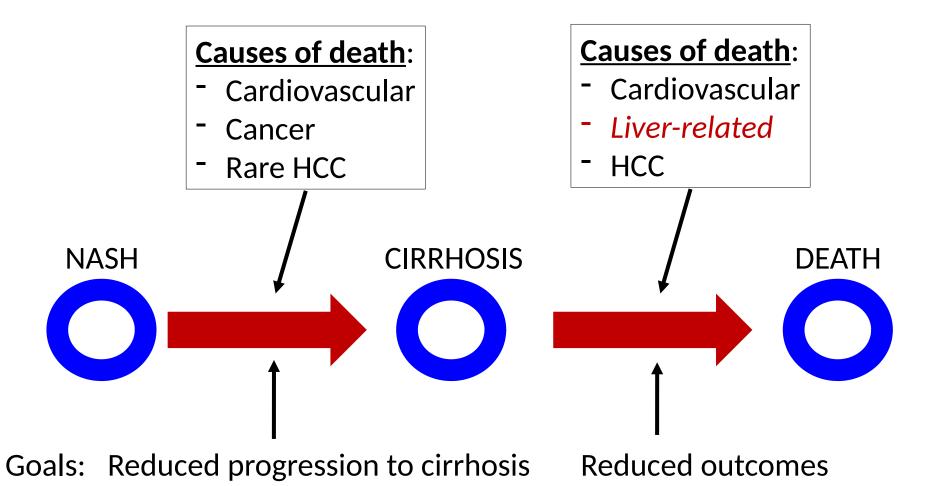
✓ Obesity

✓ Type 2 diabetes (T2D)

✓ Metabolic syndrome (MetS)

Younossi, et al. Clin Gastroenterol Hepatol 2011 Younossi, et al. Hepatology 2016

NAFLD clinical scenarios

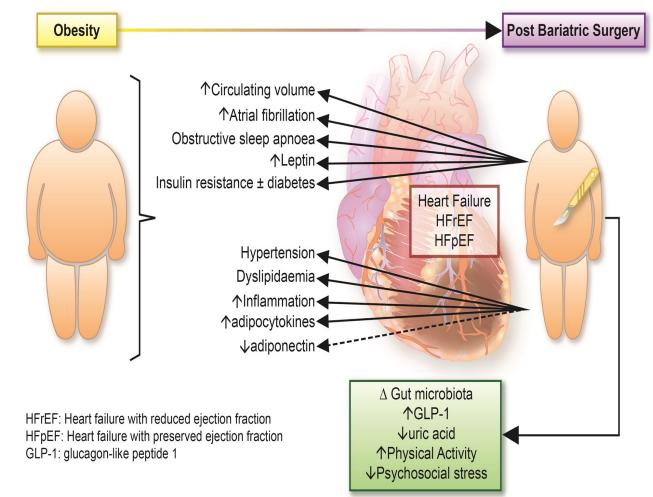




Diet and lifestyle changes



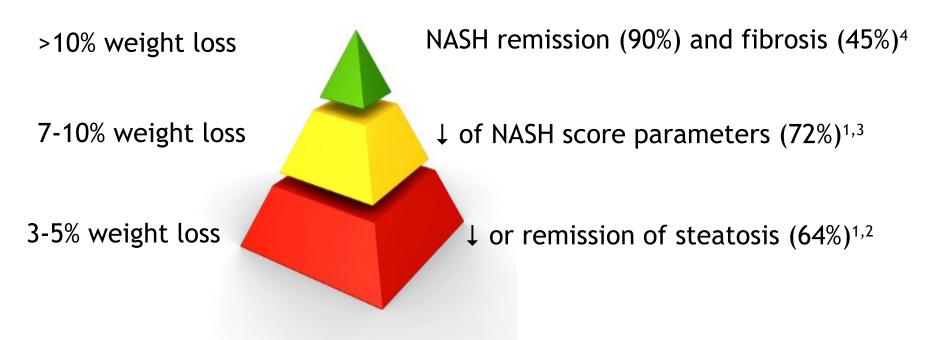
Weight loss benefits key outcomes associated with excess adiposity



Finer N. European Heart Journal, 2019

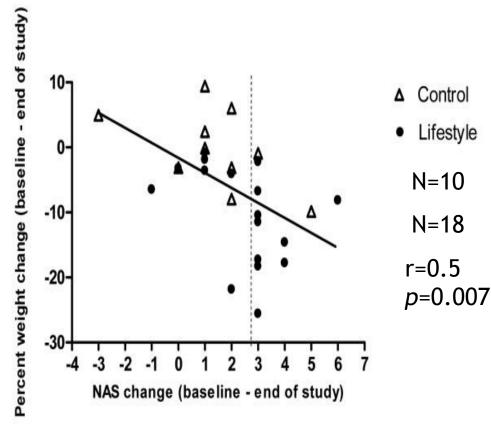
Weight loss: the cornerstone of the treatment

3 randomized and 1 cohort studies (N = 293)

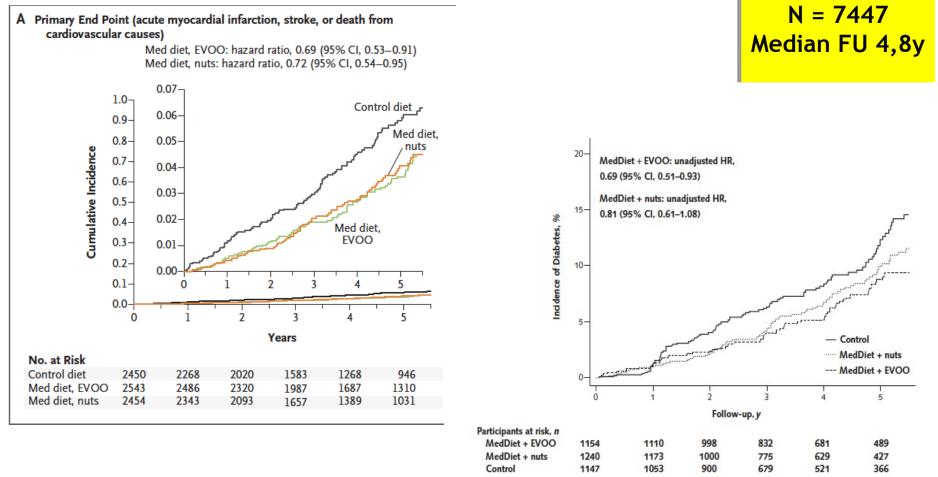


Harrison et al. Hepatology 2009; 2. Wong et al. JHepatol. 2013
 Promrat et al. Hepatology 2010; 4. Vilar-Gomez et al. Gastroenterology 2015

Effect of combined diet and exercise on liver histology in NASH

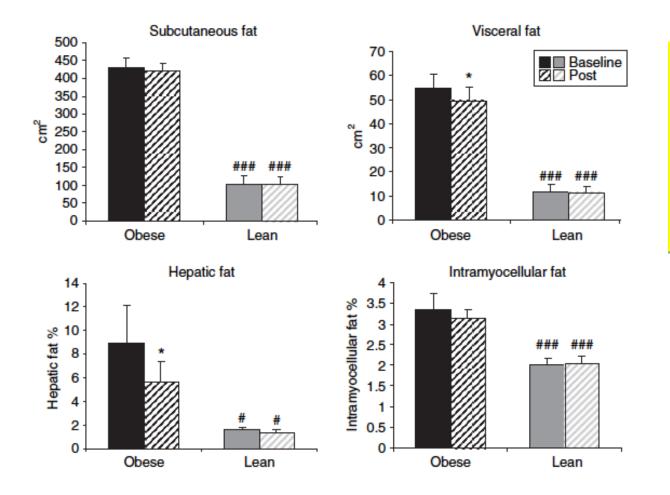


- 48 week diet and exercise intervention
- Steatosis improves with minimal wt loss but benefits to Inflammation/ballooning may require >7% body wt loss
- No effect on fibrosis



Estruch, et al. N Engl J Med 2018

Salas-Salvado, et al. Ann Intern Med 2014



N = 29 Hispanic adolescents (15 obese/14 lean) 12-week controlled aerobic exercise program

Van der Heijden, et al. Obesity 2010

Intra-hepatic fat

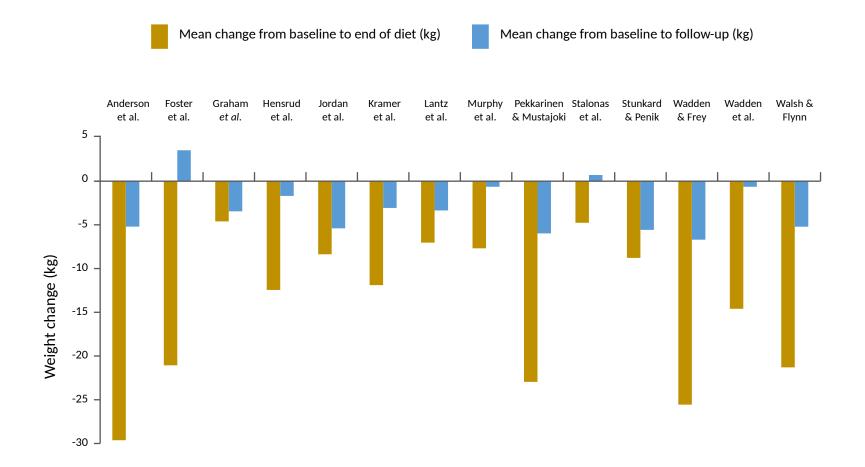
Study	Exercise	Control	Std. Mean Difference IV, Fixed, 95% CI	Weight	
,	n	n			
Hallsworth 2011	11	8		3.0%	N= 1644
Keating 2015 Group 1	12	12		5.3%	
Keating 2015 Group 3	12	12		5.6%	Physical activity-only
Sullivan 2012	12	6		4.0%	
Keating 2015 Group 2	12	12		6.0%	systematic review of 28
Lee 2013 (Aerobic vs control)	16	12		7.1%	
Lee 2012 (Resistance vs control) 16	13		7.5%	randomized clinical
Lee 2012 (Aerobic vs control)	16	13		7.6%	
Pugh 2013	6	5		2.9%	trials
Zelber-Sagi 2014	33	31		17.6%	
Lee 2013 (Resistance vs control)) 16	12		7.6%	
Johnson 2009	12	7		5.0%	
Larson-Meyer 2008	12	12		6.9%	
Shojaee-Moradie 2007	10	7		4.7%	
Shah 2009	9	9		5.2%	
Tamura 2005	7	7		4.0%	
Total (95% CI)	-0.69 [-0.9	0, -0.48]	. ◇	100.0%	
		-4 Favo	-2 0 ours exercise	2 4 Favours control	

Heterogeneity: $Chi^2 = 21.22$, df = 15 (P = 0.13); I^2 = 29% Test for overall effect: Z = 6.43 (P < 0.00001)

> The effect of physical activity on hepatic liver fat content was more prominent in young patients and patients with a higher baseline BMI

> > Orci, et al. Clin Gastroenterol Hepatol 2016

Maintaining weight loss is challenging



Mann, et al. Am Psychol 2007

<mark>N = 540</mark> FU = 7y

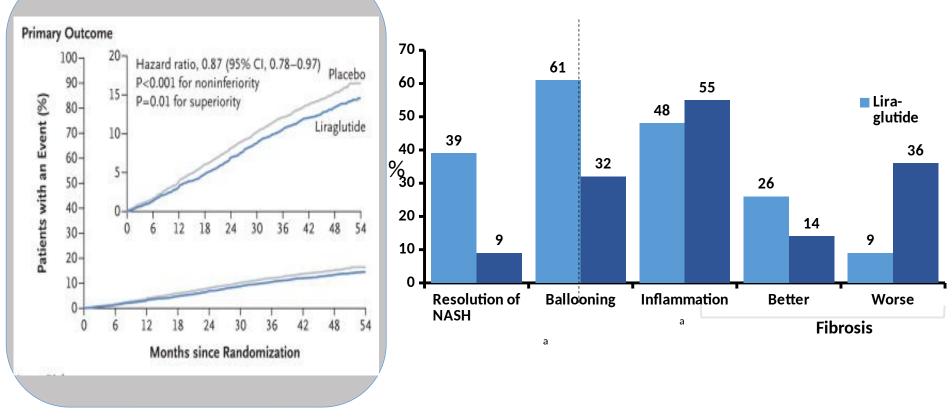
- NAFLD patients followed in a outpatients clinic of University Hospital - Federal University of Rio de Janeiro (HUCFF-UFRJ)
 - \checkmark 7% weight maintenance
 - ✓ 49% increased weight
 - \checkmark < 10% of total with reduction over 7% of initial weight

HUCFF-UFRJ 2019

Management of obesity

	Mechanism of action	Available for chronic Mean perce use loss		ntage weight	Advantages	Disadvantages	
		USA	European Union	Placebo	Drug		
Phentermine; 15–30 mg orally	Sympathomimetic	For short- term use	No	Not stated in label	Not stated in label	Inexpensive	Side-effect profile; no long-term data*
Orlistat; 120 mg orally three times a day before meals	Pancreatic lipase inhibitor	Yes	Yes	-2.6%†	-6.1%†	Not absorbed; long-term data*	Modest weight loss; side-effect profile
Lorcaserin; 10 mg orally twice a day	5-HT _x serotonin agonist with little affinity for other serotonergic receptors	Yes	No	-2-5%	-5.8%	Mild side-effects; long-term data*	Expensive; modest weight loss
Phentermine/ topiramate ER; 7·5 mg/46 mg or 15 mg/92 mg orally indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Yes	No	-1.2%	–7·8% (mid- dose) –9·8% (full dose)	Robust weight loss; long-term data*	Expensive; teratogen
Naltrexone SR/ bupropion SR; 32 mg/360 mg orally (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	-1-3%	-5-4%	Reduces food craving; long-term data*	Moderately expensive; side-effect profile
Liraglutide; 3·0 mg Injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	-3%	-7-4% (full dose)	Side-effect profile; long-term data*	Expensive; injectable

GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits



Armstrong, et al. Lancet 2016

GLP-1 agonists reduce all cause mortality, hospitalization for heart failure and improve renal status in DM

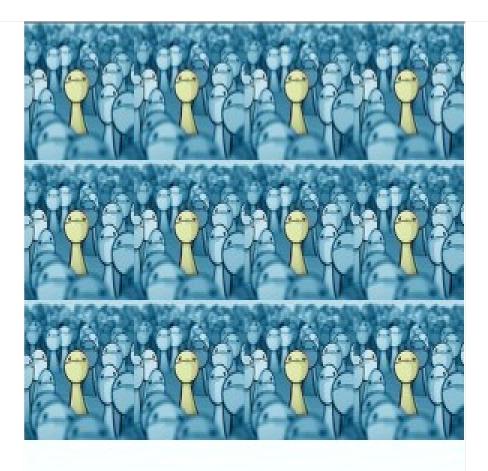
	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)		Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality						
ELIXA	211/3034 (7%)	223/3034 (7%)		0.94 (0.78-1.13)		0.50
LEADER	381/4668 (8%)	447/4672 (10%)	-	0.85 (0.74-0.97)		0.02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	*	1.05 (0.74-1.50)		0.79
EXSCEL	507/7356 (7%)	584/7396 (8%)		0.86 (0.77-0.97)		0.016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)		0.95 (0.79-1.16)		0.64
REWIND	536/4949 (11%)	592/4952 (12%)		0.90 (0.80-1.01)		0.067
PIONEER 6	23/1591 (1%)	45/1592 (3%)		0.51 (0.31-0.84)		0.008
Overall	1916/27977 (7%)	2246/28027 (8%)	\diamond	0.88 (0.83-0.95)	108 (77 to 260)	0.001
(l²=16·5%, p=0·304)			· · · · · · · · · · · · · · · · · · ·			
Hospital admission for h	neart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)		0.96 (0.75-1.23)		0.75
LEADER	218/4668 (5%)	248/4672 (5%)		0.87 (0.73-1.05)		0.14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)		1.11 (0.77-1.61)		0.57
EXSCEL	219/7356 (3%)	231/7396 (3%)		0.94 (0.78-1.13)		0.51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)		0.71 (0.53-0.94)		<0.0001
REWIND	213/4949 (4%)	226/4952 (5%)		0.93 (0.77-1.12)		0.46
PIONEER 6	21/1591 (1%)	24/1592 (2%)		0.86 (0.48–1.44)		0.59
Overall	936/27977 (3%)	1016/28027 (4%)	~	0.91 (0.83-0.99)	312 (165 to 2810)	0.028
(l ² =0.0%, p=0.595)	55-1-1 511 (5-4)		· · · · · · · · · · · · · · · · · · ·	- 5-(5 - 55)	5(5)	
Composite kidney outco	ome including macroalbu	minuria				
ELIXA	172/2639 (6%)	203/2647 (6%)		0.84 (0.68-1.02)		0.083
LEADER	268/4668 (6%)	337/4672 (7%)		0.78 (0.67-0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)		0.64 (0.46-0.88)		0.005
EXSCEL	366/6256 (6%)	407/6222 (7%)		0.88 (0.76-1.01)		0.000
REWIND				0.85 (0.77-0.93)		0.0005
REWIND	848/4949 (17%)	970/4952 (20%)	-	0.05 (0.77-0.93)		0.0004
Overall	1716/20160 (9%)	2017/20142 (10%)	\Diamond	0.83 (0.78-0.89)	62 (48 to 96)	<0.0001
(l²=0·0%, p=0·413)						
Worsening of kidney fu	nction					
ELIXA	35/3032 (1%)	41/3031 (1%)		 1.16 (0.74–1.83) 		0.51
LEADER	87/4668 (2%)	97/4672 (2%)		0.89 (0.67-1.19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)		→ 1·28 (0·64–2·58)		0.43
EXSCEL	246/6456 (4%)	273/6458 (4%)		0.88 (0.74-1.05)		0.40
REWIND	169/4949 (3%)	237/4952 (5%)		0.70 (0.57-0.85)		0.10
Overall	555/20753 (3%)	662/20762 (3%)	$ \land$	0.87 (0.73-1.03)	245 (118 to -1064†) 0.098
(l ² =42·7%, p=0·137)						,
					1/	
			Favours GLP-1 Favours		Krist	ense

receptor agonist placebo

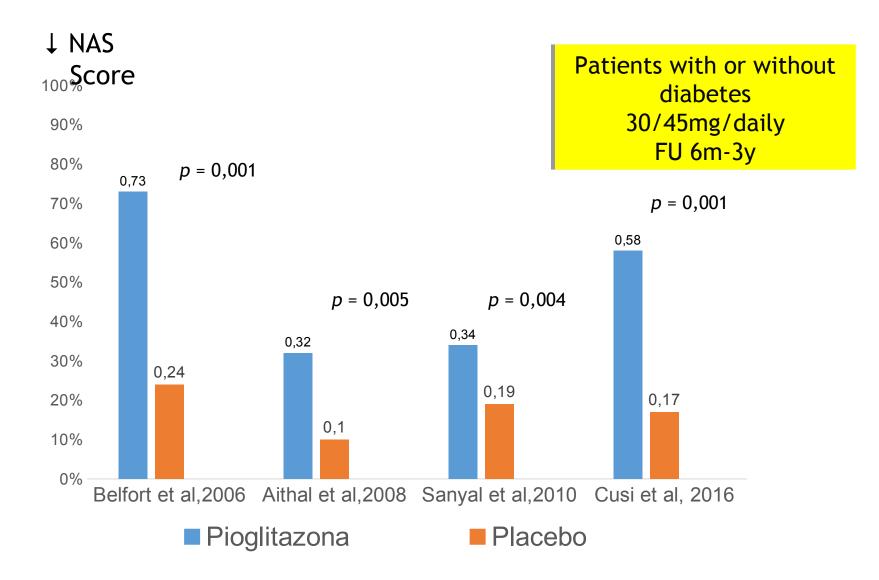
Kristensen et al. Lancet Diabetes Endocrinol 2019

	N	<i>Follow-up</i> (m)	NAFLD Outcomes
Mathuri n et al, 2009 *	381	50	48% NASH improvement Early stage fibrosis at 5y
Taitano et al,2015	160	31	90% NASH remission 60% regression of fibrosis
Lassailly et al,2015	109	12	85% NASH remission 34% regression of fibrosis
Manco et al,2016	93	12	100% NASH remission 90% regression of fibrosis

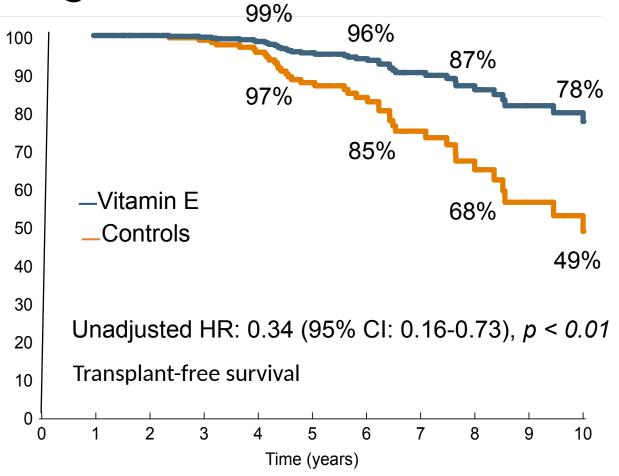
Which would be the best candidates for pharmacological treatment for NAFLD?



Randomized Studies with Pioglitazone

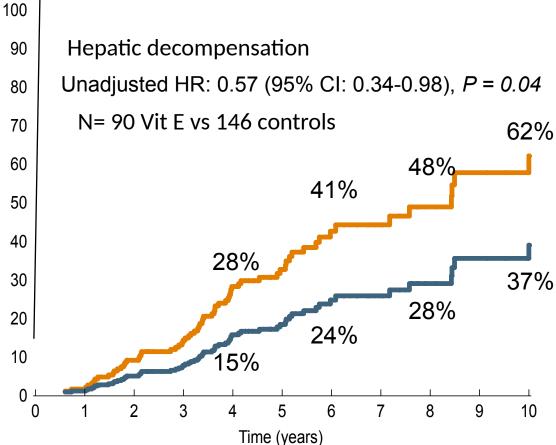


Vitamin E improves transplant free survival and decompensation rates in NASH with stage 3 or 4 fibrosis



Vilar Gomez et al. Hepatology 2018

Vitamin E improves transplant free survival and decompensation rates in NASH with F3/4



Vilar Gomez et al. Hepatology 2018

N = 132377 35-79y FU = 8y Non diabetic individuals

✓ A total of 6,555 incident diabetes (3,734 men and 2,821 women) were identified, on average, over 5.8 years of follow-up.

✓The risk of incident diabetes was significantly associated with NAFLD [HR=2.08 (men) and 2.65 (women)].

✓ Elevated ALT, AST, GGT and ALP were also significantly associated with the increased risk of diabetes.

Chen, et al. Sci Rep 2017

NAFLD - Nonalcoholic Fatty Liver Disease and diabetes

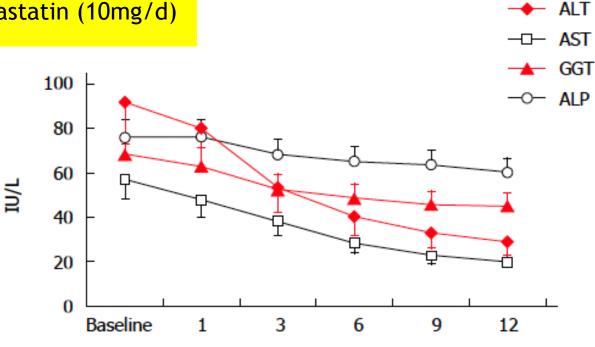
• Metformin

- ✓ First-line drug in the treatment of diabetes and prevention of pre diabetes progression
- \checkmark No proven benefit in histological parameters
- ✓ Anti-Tumor Effect Limited Human Data (Retrospective Study)

Haukeland, et al. Scand J Gastroenterol 2009 Shields, et al. Therap Adv Gastroenterol 2009 Bhalla, et al. Cancer Prev Res 2012 Zhang, et al. J Clin Endocrinol Metab 2012

NAFLD - Nonalcoholic Fatty Liver Disease and dyslipidemia

N = 20 NASH biopsy proven 12m Rosuvastatin (10mg/d)



t/mo

Kargiotis, et al. World J Gastroenterol 2015

Take home messages

- NAFLD is a highly prevalent disease.
- There is no approved drugs.
- Diet and lifestyle changes are essential.
- Pioglitazone and Vitamin E still play a role.
- Statins are underused in NAFLD patients.

