



MELANIE SUNDERLAND PHARMD STUDENT

NASH?

- Nonalcoholic steatohepatitis
 - Silent disease in early stages
 - Symptoms (advanced disease)
 - Fatigue
 - Weakness
 - Weight loss
 - 2 to 5% of Americans
 - Highest incidence in middle age
 - Resembles alcoholic hepatitis but occurs in people who drink minimal alcohol

NASH: Causes

- Cause unclear
 - Proposed causes:
 - Insulin resistance
 - Toxic inflammatory proteins released by fat cells
 - Oxidative stress
- Risk factors:
 - Obesity
 - Dyslipidemia
 - Diabetes

NASH: Progression

• Non alcoholic fatty liver disease



Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005166.

NASH: Treatment



GASTROENTEROLOGY 2008;134:1682-1698

NASH: Treatment



GASTROENTEROLOGY 2008;134:1682-1698

Patient	Adults with symptomatic NASH
Intervention	Metformin
C omparator	Placebo
Outcome	 Efficacy Mortality Progression to cirrhosis Symptoms Liver enzymes Imaging changes Histology changes Safety

Search Strategy

Databases	Medline, Google Scholar, PubMed, EMBASE, Google
Search Terms	NASH, metformin, hepatitis, fatty-liver disease
Limits	English, adults, NASH, prospective
Results	 1 Cochrane review 2 RCTs 3 Prospective non-RCT

Non-randomized Studies

	Study Design	Patients	Intervention	Primary Outcome
Marchesini et al. 2001	OL, SA	N=20	<pre>**Metformin 1.5g/day X 4 mths</pre>	ALT change (U/L) -0.5 vs -0.14 p< 0.05
de Oliveira et al. 2008	OL, SA	N=20	Metformin 1g/day & NAC X 12 mths	Steatosis and fibrosis grading p< 0.05
Loomba et al. 2008	OL, SA	N=26	Metformin 2g/day X 48 wks	NASH activity index 8.2→ 5.9 p< 0.001

**Matched to 6 patients with NASH not on metformin

Marchesini et al.



Alanine transaminase concentrations over time in patients with non-alcoholic steatohepatitis The Lancet 2001 Sept; 358



Figure 2 Fibrosis in 20 patients with non-alcoholic steatohepatitis at time baseline of biopsy and after 12 months of treatment with N-acetylcysteine plus metformin. Histopathological analysis demonstrated a marked decrease in liver fibrosis after treatment. (\blacksquare), Basal; (\blacksquare), after 12 months. Aliment Pharmacol Ther 2004; 19: 537–544.

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Metformin in the treatment of patients with non-alcoholic steatohepatitis

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Uygun *et al.*

Design	RCT		
Patients	Adults with NASH (n=36) Many exclusions including diabetes mellitus		
Intervention	Metformin 850mg PO BID plus dietary treatment X 6 months		
Comparator	Dietary treatment alone X 6	months	
Outcomes	 Efficacy Liver enzymes Insulin resistance Body mass index Histology 	Toxicity -Serum lactate - ADRs	

Patients: Baseline

	Control (n=17)	Metformin (n=17)
Sex- males (%)	11 (65)	10 (59)
Age (range)	39.8 (22–64)	41.5 (23–61)
ALT (U/L)	72.8 +/- 31.2	83.5+/- 24.6
AST (U/L)	48.1 +/- 26.3	57.9 +/- 17.3
Index of insulin resistance	1.83 +/- 0.74	2.53 ± 0.98
BMI (kg/m2)	30.1 ± 3.4	28.4 ± 3.9

Outcomes: Mean Change

Parameter	Control Mean +/- SD (%)	Metformin Mean +/- SD (%)	P-value
ALT (U/L)	-17.4 +/- 14.1	-37.1 +/- 22.2	0.003
AST (U/L)	-6.8 +/- 5.9	-22.1 +/- 14.3	0.0001
Index of insulin resistance	-0.02 +/- 0.03	-1.15 +/- 0.82	0.001
BMI (kg/m2)	-1.9 +/- 2.1	-2.4 +/- 1.9	0.01

Outcomes: Biopsy Results

	Control			Metformin		
	0 mths	6 mths	P-value	0 mths	6 mths	P-valve
Necro- inflammatory activity	1.41 +/- 0.6	1.3 +/- 0.48	0.62	1.41 +/- 0.61	1.15 -/+ 0.68	0.31
Fibrosis	1.05 +/- 1.1	1.12 +/- 1.1	0.91	0.94 +/- 1.02	0.92 +/- 1.03	0.96

** p > 0.05 between control and metformin

Outcomes: ADRs

- No metformin discontinuation due to ADRs
- Mild gas/bloating in metformin group (4/17)
- Moderate abdominal pain in metformin group (2/17)
- No statistical change in lactic acid

Critique

- Allocation concealment unclear
- Unblinded
- Few patients → powered?
 No sample size calculation
- 6month treatment period
- Generalizability
- Comparison to diet

Conclusions

- With 6 months of metformin therapy:
 - Improvement in liver enzymes and reduction of insulin resistance
 - No significant histological changes noted
- More studies with more patients are required

Alimentary Pharmacology & Therapeutics

Clinical trial: insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis

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Aliment Pharmacol Ther 28, 200–208

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Idilman*et al.*

Design	RCT, SC		
Patient	Adults diagnosed with NASH		
Intervention	Metformin 850mg PO BID or rosiglitazone 8mg PO daily plus diet and exercise X 48 weeks		
Comparator	Diet and exercise alone X 48 weeks		
Outcome	 Efficacy Liver enzymes BMI Insulin and glucose levels Histological features 	Toxicity - ADRs	

Patients

	Control (n= 25)	Insulin sensitizer (n= 48)
Age	45.8 +/- 10.4	47.0 +/- 8.3
Sex- males (%)	9 (36)	21 (44)
Dyslipidemia hx (%)	5 (20)	10 (21)

Outcomes

	Meformin		
	Baseline	48 weeks	P-value
AST (U/mL)	49.7 +/- 27.0	34.4 +/- 21.6	0.047
ALT (U/mL)	82.9 +/- 52.9	50.0 +/- 37.1	0.017
BMI (kg/m2)	30.8 +/- 3.9	29.0 +/- 3.5	< 0.001
FPI (microU/mL)	18.2 +/- 12.2	12.0 +/- 11.4	0.023



**no significant difference between the two groups (P > 0.05)



**no significant difference between the two groups (P > 0.05)

Outcome: Change from Baseline

	Control P-value (n=25)	Metformin P-value (n=24)
BMI (kg/m2)	0.002	<0.001
FPI (microU/mL)	>0.05	0.023

Outcome: Histology

Control (n=8)	Treatment (n=21)
No statistical change in histological parameters	 Statistically significant decrease in: steatosis ballooning NAS score
	No statistical change in other histological parameters

Outcome: ADRs

- No significant ADRs reported
- No dropouts

Critique

- Few patients \rightarrow powered?
 - No sample size calculation
 - Few patients underwent biopsy
- Allocation concealment unclear
- Unblinded
- Inadequate statistical tests and inappropriate conclusions
- 48 week treatment period
- Generalizability
- Comparison to diet/exercise

Conclusion

- No statistical difference in ALT/AST between treatment and control
- Statistical decrease in fasting insulin in the metformin group
- Difficult to interpret histology results due to low number in the control group
- Inadequate statistics to compare groups

Overall Conclusion

Mortality	?
Symptoms	?
LFT improvement	
Imaging improvement	?
Histology improvement	?
Progress to cirrhosis	?
ADRs	

Conclusion

- Mechanism of metformin seems plausible for treatment of NASH
- Evidence doesn't support its use at this time
- Larger and longer trials required

QUESTIONS?



Extra slides

Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis (Review)

Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F



	Metformin P-value (n=24)	Control P-value (n=25)
AST (U/mL)	0.047	0.002
ALT (U/mL)	0.017	<0.001
BMI (kg/m2)	<0.001	0.002
FPI (microU/mL)	0.023	>0.05
Cholesterol (mg/dL)	0.287	0.001

Aliment Pharmacol Ther 28, 200–208

 "In this study, in contrast to the diet and exercise group, a significant improvement in histological features was also observed in the treatment group. The histological features of steatohepatitis, including steatosis and ballooning, were reduced only in the treatment group."