UPDATE FROM THE NIH

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Kennedy's Disease Association Meeting

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CURRENT STUDIES AT THE NIH

- 14-N-0099- Evaluation of hepatic function in patients with spinal and bulbar muscular atrophy
- Quality of Life for Spinal Bulbar Muscular Atrophy- Robert Guber

National Institute of Neurological Disorders and Stroke
National Institutes of Health

UPDATE ON LIVER STUDY

- Patients with SBMA tend to have mildly elevated liver enzymes that may signify excess fat in the liver. These elevated liver enzymes may also be high due to breakdown of muscle that occurs in SBMA patients.

- Fatty liver changes in the general population are known to occur often due to excess alcohol intake, obesity, and high cholesterol.

- To understand any possible relationship between SBMA patients, SBMA carriers, and fatty liver disease we will evaluate for changes in liver function in SBMA patients and healthy individuals (controls).

STUDY POPULATION

- 15 men with SBMA
- 15 female SBMA carriers
- 15 male age matched controls
- 15 female age matched controls
- 15 individuals with motor neuron disease

PROCEDURES

- Blood work, liver and muscle imaging, liver biopsies, BDI, Diet history questionnaire II (DHQII)
- Liver biopsy is optional; qualifications for liver biopsy
  - ALT >31 or AST>30 on 2 separate measurements
  - BMI under 30
  - Imaging changes

- We have had 3 patients volunteer to do the liver biopsy

IMPORTANCE OF LIVER BIOPSY

- Helps identify Non Alcoholic Fatty Liver Disease (NAFLD) and make the distinction from Non Alcoholic Steatohepatitis (NASH)
- Staging of the disease
- Pattern of fatty deposition
- Mechanism of toxicity

WHERE ARE WE NOW

- 15 SBMA males currently enrolled
- 15 SBMA carriers currently enrolled
- 6 Healthy Controls enrolled
- 1 Healthy Female Control enrolled
- We also have 2 males and 2 females to come in for the study in Nov/ Dec.

PRELIMINARY FINDINGS –SBMA PATIENTS

Liver MRS TG content % (avg)	Mean +/- SD	Range	Reference Range
Dome	14.9% (+/- 12.9%)	3.3-44%	<5%
Inferior	13.5% (+/- 13.0%)	3.3-44%	<5%
Left	11.8% (+/- 11.6%)	2.3-36%	<5%

PRELIMINARY FINDINGS- SBMA PATIENTS (CONTINUED)

- Average ALT: 41 IU/L (+/-17)- normal range= 0-41 U/L
- Average AST: 35 IU/L (+/- 11)- normal range= 0-40 U/L
- Abdominal Ultrasound c/w hepatic steatosis in 11/14 studies (79%)
- 8/14 meet criteria for performing the liver biopsy.
- Out of the 8 that were eligible:
  - 3 completed the biopsy
  - 2 had confounding factors
  - 3 declined

RESULTS OF PATIENTS WHO AGREED TO LIVER BIOPSY

- Patient #1- ALT 80; Fatty Liver Disease with mild fat, mild inflammation, mild liver injury; no thickening or scarring of tissue.
- Patient #2- MRI 10%, ALT 32; moderate fatty liver disease with minimal inflammation and no fibrosis
- Patient #3- MRI 21%; ALT 33; fatty liver disease with moderate fat, mild chronic inflammation, prominent liver cell injury and blood plasma thickening.

Increased Hepatic Steatosis and Insulin Resistance in Mice Lacking Hepatic Androgen Receptor

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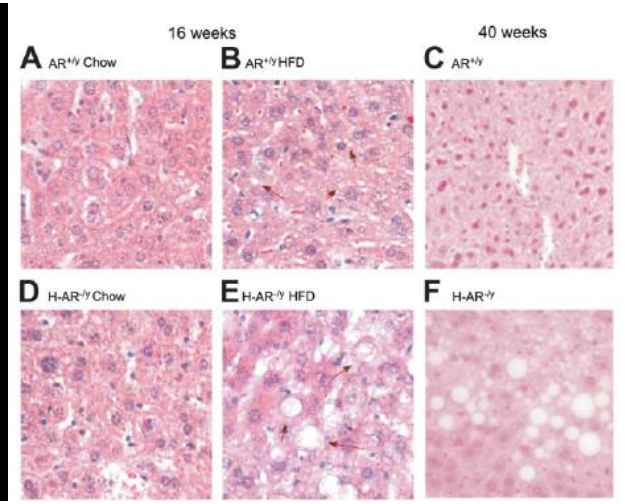
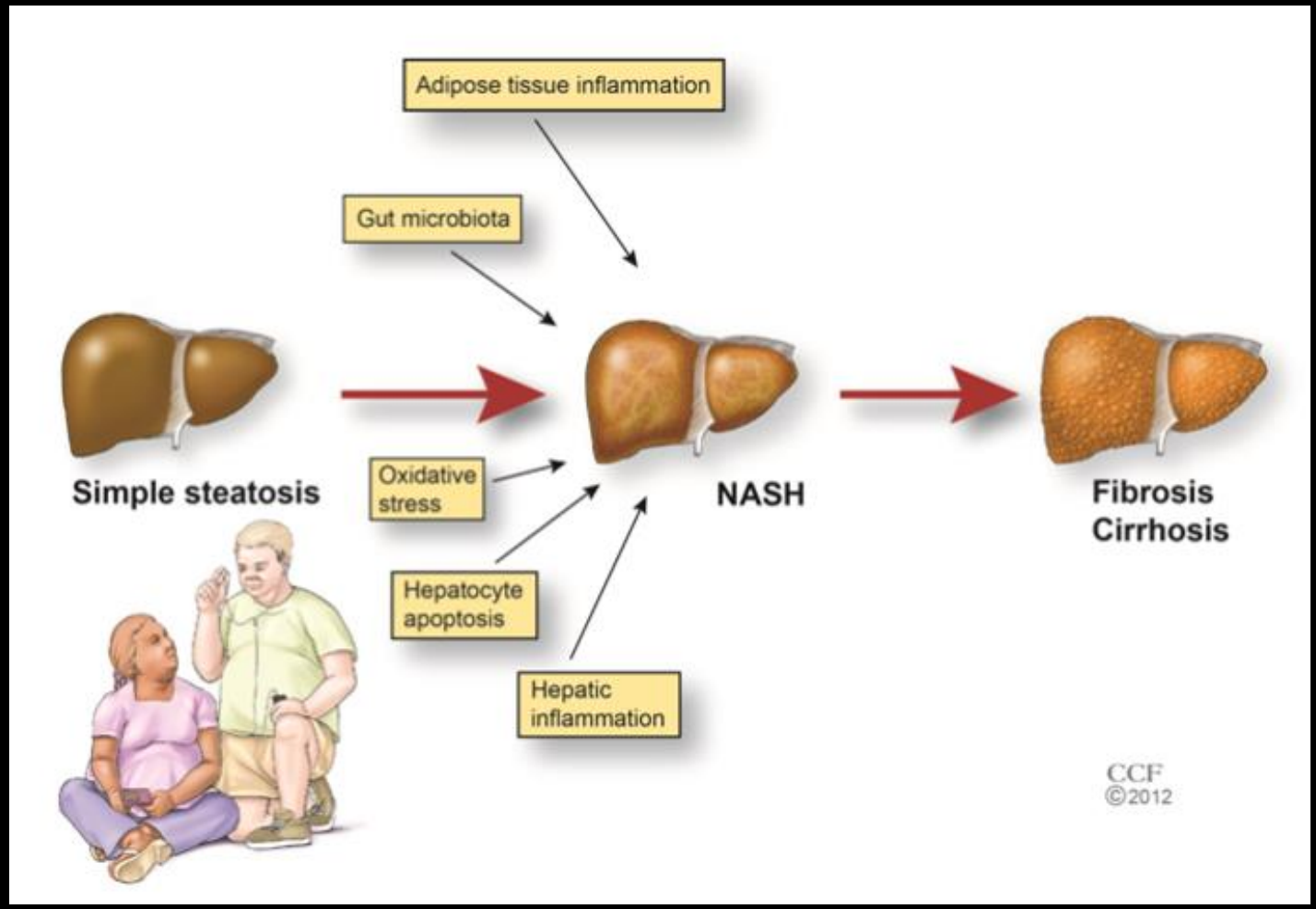


Table 1. Metabolic Parameters During Fasting in $AR^{+/y}$ and $H\text{-}AR^{-/y}$ Mice Fed Chow or HFD at 16 Weeks Old

	$AR^{+/y}$		$H\text{-}AR^{-/y}$	
Group	Chow Diet	High-Fat Diet	Chow Diet	High-Fat Diet
Triglyceride (mg/dL)	20.1 ± 2.6	27.3 ± 3.3	30.7 ± 2.4	35.2 ± 2.6*
NEFA (mEq/L)	0.86 ± 0.07	0.76 ± 0.11	0.96 ± 0.08	0.71 ± 0.13
Cholesterol (mg/dL)	113.2 ± 3.4	142.6 ± 5.1	105.7 ± 8.3	137.3 ± 10.6
Leptin (ng/mL)†	2.3 ± 0.2	9.6 ± 2.1	3.2 ± 0.1	15.1 ± 3.4‡
Adiponectin (μg/mL)	2.13 ± 0.09	nd	1.42 ± 0.19§	nd
IGF-1 (ng/mL)	342.9 ± 33.6	nd	156.7 ± 18.6	nd
GH (ng/mL)	62 ± 8.1	nd	240 ± 36.4	nd
Testosterone (ng/mL)	3.34 ± 0.59	nd	3.49 ± 0.91	nd

Fasting refers to an overnight fast. Data are mean ± SEM of 6-7 mice per group. *$P < 0.05$ $AR^{+/y}$ (HFD) versus $H\text{-}AR^{-/y}$ (HFD). †Leptin was assayed in fed animals. ‡$P < 0.01$ $AR^{+/y}$ (HFD) versus $H\text{-}AR^{-/y}$ (HFD). §$P < 0.05$ $AR^{+/y}$ (chow) versus $H\text{-}AR^{-/y}$ (chow). $P < 0.01$ $AR^{+/y}$ (chow) versus $H\text{-}AR^{-/y}$ (chow). nd, not determined.

Liver Disease in SBMA?

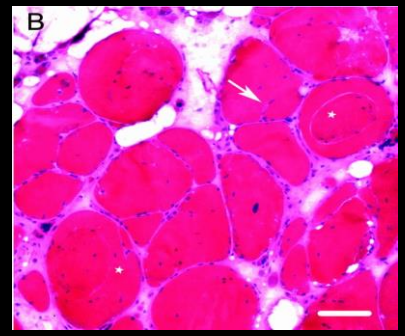


From American college of Gastroenterology, Maim Alkhouri et al., 2012

MECHANISM?

From Adachi et al., Brain 2005

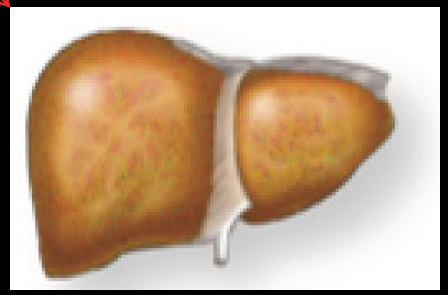
From Preisler et al., Neurology 2009



↓↑ AR

Metabolism / activity

↓↑



CONCLUSIONS

- Evidence of fatty liver is found in 80-90% of SBMA patients.
- Some patients with fatty liver were found to have steatohepatitis (NASH).
- Patients may be at risk for liver changes secondary to hepatic AR insensitivity.
- Unclear relationship with disease mechanism

FUTURE STUDIES

-Analysis of SBMA and disease control liver biopsies.

-Molecular and pathological studies of the tissue for AR mediated toxicity.

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