ASSESSMENT OF LIVER STIFFNESS IN THE US POPULATION BY ULTRASOUND ELASTOGRAPHY

Research Contract Opportunity Concept Review

Gary Murray
Division of Metabolism and Health Effects, NIAAA
Alcoholic Liver Disease

Steatosis
- 90-100% heavy-drinkers

Alcohol

Steatohepatitis
- 10-35%

Fibrosis/Cirrhosis
- 8-20%

Fibrosis/Cirrhosis
- 8-20%

Genetics
- Poor nutrition
- Co-existing diseases
- Gender
- Race/ethnicity

Severe Alcoholic Hepatitis

Hepatocellular Carcinoma
- 2%

Gastroenterology, 1978;
Alcohol and Alcoholism 1996
Alcoholic Liver Disease: A Mosaic of Diseases

- Alcoholic Steatosis (Fatty Liver): ~90-100% of AUD
- Alcoholic Steatohepatitis: (20%)
- Alcoholic Hepatitis
- Alcoholic Cirrhosis: 10%
- Subclinical

High mortality: 10,000 Deaths in 2003
Extent of the Problem of Alcoholic Fatty Liver

What do we know and how do we know it?

- Fatty liver is the earliest and most benign stage of alcoholic liver disease (ALD)
- 7.1 percent reported that they engaged in heavy drinking in the past month (SAMHSA, 2012)
- 90% of those who consume alcohol excessively develop fatty liver.

- Lefkowitch (2005)
- Lieber (1965)
- Mathurin et al. (2007)
- Lefkowitch (2005)
  i. “Morphology of Alcoholic Liver Disease” is an excellent description of morphological characteristics of ALD and includes a discussion of the differential diagnosis between NASH and ASH but no quantitative assessment of frequency
Extent of the Problem of Alcoholic Fatty Liver

What do we know and how do we know it?

- Fatty liver is the earliest and most benign stage of alcoholic liver disease (ALD)
- 7.1 percent reported that they engaged in heavy drinking in the past month (SAMHSA, 2012)
- 90% of those who consume alcohol excessively develop fatty liver.

- Lefkowitch (2005)
- Lieber (1965)
- Mathurin et al. (2007)

- Lieber (1965)
  
  i. Performed liver biopsies on five individuals asked to drink heavily and studied under metabolic ward conditions in order to show that fat accumulates relatively rapidly in the liver after heavy drinking for 2 to 3 weeks
Extent of the Problem of Alcoholic Fatty Liver

What do we know and how do we know it?

• Fatty liver is the earliest and most benign stage of alcoholic liver disease (ALD)
• 7.1 percent reported that they engaged in heavy drinking in the past month (SAMHSA, 2012)
• 90% of those who consume alcohol excessively develop fatty liver.

• Lefkowitch (2005)
• Lieber (1965)
• Mathurin et al. (2007)

• Mathurin et al.
  i. Biopsies of individuals in hospital with alcohol-use disorder
  ii. Macrovesicular steatosis, the first and most common pathologic change seen with chronic alcohol ingestion occurs in up to 90% of heavy alcohol users [Mathurin et al. 2007].
What does the presence of fatty liver tell us?

The presence of fatty liver alone does not predict more serious sequelae, but...

- Teli et al. (1995)
  - Demonstrated convincingly that, with continued drinking, “Pure” fatty liver was likely to progress to more severe symptoms of ALD
- Lucey (2009)
  - Abstaining from alcohol use may result in significant improvement in the milder pathology
- Lischner (1971)
  - Abstinence leads to resolution of alcoholic fatty liver and alcoholic hepatitis
- Powell (1968)
  - Abstinence is associated with improved survival in alcoholic cirrhotic patients with decompensated liver function

What’s New?

The NHANES III conducted between 1988 and 1994 is a cross-sectional national examination study conducted in the United States by the National Center for Health Statistics. Part of the study included ultrasonography data from 12,454 adults participants. Lazo et al (2014) recently published an analysis of these results.

American Journal of Epidemiology


Lazo and her colleagues were able to determine the presence of hepatic steatosis using ultrasonography... in the absence of elevated alcohol consumption
What is Liver Stiffness

It is well established that fibrosis increases liver stiffness.

**What is liver stiffness?**

- Liver palpation is a routine medical practice that has been used since the beginning of medicine to assess liver stiffness.
- Palpation suffers from major limitations
  - Highly subjective
  - Operator dependent
  - Sometimes impossible to perform
- Vibration-controlled transient elastography (VCTE) and magnetic resonance elastography are new quantitative tools that are useful for assessing liver stiffness.
What is Elastography

What is it and why do we need it?

- The evaluation of liver fibrosis is of major importance for the management and the prediction of prognosis for chronic liver disease
- Progression to cirrhosis is associated with a risk of liver related complications, hepatocellular carcinoma (HCC), and mortality.
- Liver biopsy is currently the gold standard in assessing liver histology.
- Although percutaneous liver biopsy is in general a safe procedure, it is costly and does carry a small risk for complication.

Other relatively non-invasive tests such as serologic testing will detect significant to severe fibrosis and cirrhosis

**LIVER STIFFNESS**: Through palpation, Vibration-controlled transient elastography (VCTE) and magnetic resonance elastography are useful for assessing
What is Elastography

What are Vibration-controlled transient elastography (VCTE) and magnetic resonance elastography?

- Noninvasive liver stiffness measurement (LSM), or elastography, by ultrasound-based VCTE using is an FDA-approved technique that calculates liver stiffness expressed in kilopascals (kPa).

- Magnetic resonance elastography uses propagating mechanical shear waves (range, 20–200 Hz) to probe the mechanical properties of various organs during an MRI examination and is not currently FDA-approved.
Extent of the Problem of Alcoholic Fatty Liver

What do we hope to learn through the Elastography Program

• Fatty liver is the earliest and most benign stage of ALD and can progress to fibrosis and more severe clinically relevant disease.

• Elastography in the non-institutionalized U.S. population would provide a (vastly) improved estimate of the problem compared to current data.

• Unique data set: the non-institutionalized U.S. population may be more generally representative of the extent of alcohol-related liver disease (compared with most published studies that rely on hospital data only)
Contract Proposal

1. Develop a contract with the National Center for Health Statistics to perform ultrasound on the non-institutionalized population in the U.S.

2. Introduce questions appropriate for determining the extent of alcohol use in this cohort.

3. Perform this additional testing in cooperation with the NIDDK who are interested in broadening and modernizing the previous results.
Specific Aims:

1. To measure liver stiffness using ultrasound elastography in representative US adults aged 18 +.
2. To link these measurements to other NHANES data to provide estimates of the prevalence of liver fibrosis and fatty liver by key socio-demographic and clinical characteristics.
3. To provide estimates of liver fibrosis and fatty liver by type of liver disease: viral, alcohol-related, non-alcoholic liver disease.

Issues:

1. How many subjects will be included?
2. Can these be clearly stated and articulated?
3. Does the contract encompass the analysis of the results?
Benefits to NIAAA and the Community

- Fill the information gap on the extent of alcohol-related liver disease in the context of all other causes of liver disease (NAFLD and viral). Specific gaps that this contract will fill and the specific questions that would be answered still need to be developed.

- Information on demographic variation in this non-institutionalized study population is critical for designing better outreach to the most severely affected communities.
The National Health and Nutrition Examination Survey (NHANES) : Monitoring Nation’s Health and Nutrition
Overview

• NHANES is a continuous cross-sectional survey of the US civilian, non-institutionalized population

• Unique: Interviews + Examination on representative sample

• Contact with participants at:
  • Doorstep recruitment
  • Home Interview
  • Examination at Mobile Exam Center (MEC)
  • Post-MEC components

• No longitudinal follow-up
NHANES Sample

- Civilian, non-institutionalized household population in the United States
- All ages (5000 individuals each year)
- Oversample certain groups
  - Older persons aged 60+
  - Low income whites
  - African Americans
  - Hispanics
  - Asian Americans (2011-14, planned for 2015-18)
NHANES: Complex Sample Design

A four-stage stratified nationally representative sample
Field interviews: Household contact

Screener

Home Interview

Traditional CAPI with portable computer

Info on: health conditions, health care use, prescription meds use, dietary supplements use…
NHANES Mobile exam center
MEC Exam: Standardized Data Collection
NHANES topics

• Cardiovascular disease
• Diabetes, kidney disease
• Bone status, osteoporosis
• Obesity, body composition
• Oral health
• Hearing, balance
• Alcohol and Smoking
• Vision, ophthalmology
NHANES topics (Cont)

• Nutrition
• Allergies
• Mental health
• Risk behaviors
• Reproductive health
• Environmental exposures
• Infectious diseases, STDs
• Prescription medications
Advantages of the Contract Mechanism

• Window of Opportunity: NHANES currently has a number of studies “cycling off” the survey and thus have the capacity in 2015-16 to begin a pilot with full implementation of the survey in 2017-18.

• Unique data set: non-institutionalized population in the U.S. not just those with AUD who appear at a hospital

• Cross-agency cooperation: Joint funding by NIDDK and NIAAA will reduce costs while maximizing the benefit to the liver research field and improve coordination between all interested parties including the CDC, NIAAA (DEPR and DMHE) and NIDDK.

• Targeted information: This is an effort to obtain targeted information that NIAAA is seeking and not an investigator initiated research project.
3. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. (1995); *Lancet* **346**: 987-990
For follow-up suggestions, please contact:

Gary Murray, DMHE
gary.murray@nih.gov
(301) 443-9940

Rosalind Breslow, DEPR
rosalind.breslow@nih.gov
(301) 594-6231