Nutrition and Metabolism in Hepatitis C Infection

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Understanding Nutrition and Metabolism in HCV Complicated by

- Genotype of HCV
- Degree of liver dysfunction
- Substance use
- HIV co-infection
  - Treatment of HIV infection
- Life style issues
  - Housing insecurity
  - Food insecurity
  - Dietary quality
  - Alcohol use

Insulin/Glucose Abnormalities in HCV

- Diabetes more common in HCV than in HBV
  - In young lean patient with no family history
- Glucose abnormalities in
  - 5.8 % of HCV-HIV coinfected patients
  - 2.8% of HIV mono-infection

- Kotler 2008

HCV and HIV

- HCV
  - Insulin Resistance
  - Low TC and LDL
  - Prothrombotic changes
    - P selectin
    - Endothelial dysfunction
  - Low CRP
  - Fat atrophy
- HIV
  - Insulin resistance
  - Low HDL
  - Prothrombotic changes
    - D-dimer
    - Endothelial dysfunction
  - High CRP
  - Increased trunk fat
  - Fat atrophy

Kotler 2008,
McGovern 2006

HCV, HIV and ART

- Insulin resistance
- Low HDL
- High or low CRP (depending on degree of liver dysfunction?)
- Prothrombotic changes
  - D-dimer, P-selectin
  - Endothelial dysfunction
- Increased trunk fat
- Fat atrophy

- Metabolic effects of ART (varies with agent)
  - Increased TG, TC, low HDL

HCV Genotype 3 & Steatosis

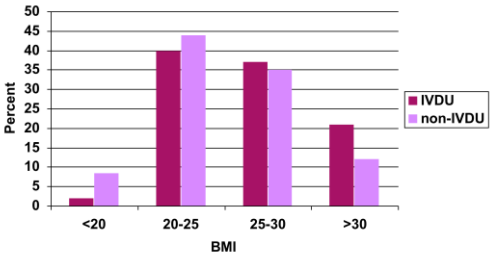
- Low TG
- Low TC
  - ? Mediated indirectly by more severe steatosis
  - Or directly by alterations in B lipoprotein production and secretion of VLDL
- HIV exacerbates abnormalities seen with GT 3

Prevalence of Overweight in HIV

BMI	Women	Men
< 20 kg/m²	10%	5%
20-25 kg/m²	30%	40%
25-30 kg/m²	30%	35%
> 30 kg/m²	30%	20%

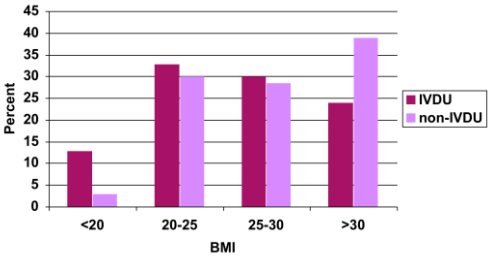
NFHL data, 2008

Overweight and Underweight in HIV-Infected Men



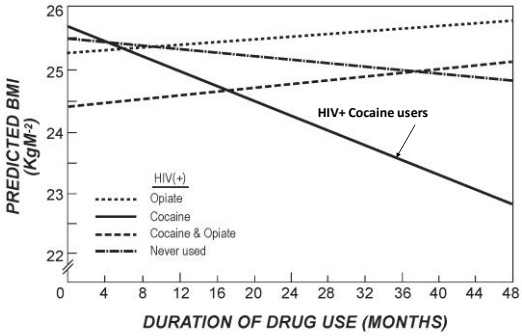
Source NFHL, n=276

Overweight and Underweight in HIV-Infected Women



Source NFHL, n=140

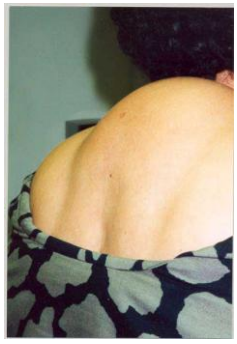
Change in BMI in relation to drug use
over 48 months in HIV-infected men



Forrester, 2008

Nutritional Compromise
may be Under-Nutrition or Over-Nutrition

- **Under-nutrition**
  - Access to food
  - Physical barriers to intake
  - Malabsorption
  - Physical activity
  - Alterations in metabolism
  - Co-morbidities
  - Effects of specific drugs
- **Over-nutrition**
  - Food insecurity
  - Dietary quality
  - Physical activity
  - Alterations in metabolism
  - Effects of specific drugs



Over-nutrition

Associated with:

- Food insecurity
- Dietary Quality
- Low level of education (surrogate of economic status)
- Decreased viral demands with suppression of viral load (in HIV and ? In HCV)
- Can we differentiate HIV-lipodystrophy from obesity with fat atrophy?

Hendricks, 2008

Predictors of Steatosis in HCV

- **BMI > 30 kg/m²**
- Increased viral load
- **Increased glucose**
- **Lipohypertrophy (increased visceral fat)**
- Age
- Alcohol use (? Direct or mediated through empty calories)
- Genotype 3
- HIV infection
- (Effective ART decreases steatosis)

Ryan 2001
Woreta 2011
Borghi 2008
Bani-Sadr 2006

Predictors of Fibrosis in HCV

- **Age**
- Low CD4
- Chronic HCV
- Alcohol use
- Increased ALT
- **Increased TG**
- Low TC
- **Increased HOMA**
- Use of D4t

- Blanco 2009

Treatment of HCV and Glucose

- Predictors of SVR (rapid VR)
  - Genotype 1 and 4
  - RNA < 400,000
  - **HOMA > 3**
- Diabetes (defined as FBS > 100 mg/dl)
  - Associated with relapse after HCV treatment

- **Nasta 2008**
- **Sulkowski 2009**

Treatment of HCV Improves HOMA-IR

- Independent of
  - Age
  - Gender
  - Ethnicity
  - BMI
  - Duration of HCV
  - Fibrosis
- Adds credibility to the role of HCV in producing IR/ DM

- Delgado Borrego 2010

Lipids and HCV Treatment

- LDL and TC in normal range have positive predictive value for SVR in HCV mono-infection
- In HIV Co-Infected:
  - Significant association between pre-treatment lipids (TC, HDL, TG) and steatosis but not fibrosis and no association with SVR

- Petit 2010; Clark

Treatment of HCV Alters Lipid Profile

- With treatment of HCV
  - Increased LDL
  - Increased TC
  - During treatment TC decreases further but increases after SVR
  - Post treatment levels may raise concern for CVD
- Response seen only in HCV treatment responders
  - Abnormalities persist in nonresponders

- Corey 2009
- Wagner 2010

Concerns about Nutritional/ Metabolic Status in HCV

- Bi-directional relationship:
  - HCV associated with abnormal lipids and glucose metabolism
  - Progression of HCV associated with presence of abnormal lipid and glucose metabolism
- As with HIV, treatment and longer survival permit development of co-morbidities of concern:
  - Diabetes
  - Metabolic Syndrome
  - Cardiovascular disease

Mortality associated with Metabolic Syndrome in HIV

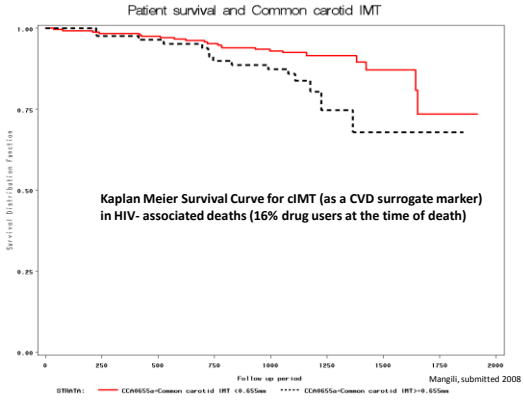
Adjusted Cox proportional hazards of mortality for high triglycerides and metabolic syndrome before and after 36 months follow-up

	Adjusted hazard ratio (95%CI)*	p-value
High triglycerides ≤36 months	1.03 (.55, 1.94)	.924
High triglycerides >36 months	**2.96 (1.44, 6.08)**	**.003**
Metabolic syndrome ≤36 months	.96 (.51, 1.82)	.900
Metabolic syndrome >36 months	**2.64 (1.33, 5.22)**	**.006**

*Adjusted for age, gender albumin, current smoker and CD4<200

45% of this cohort acquired HIV through Injection drug use

Jarrett in press, 2011



Kaplan Meier Survival Curve for cIMT (as a CVD surrogate marker) in HIV- associated deaths (16% drug users at the time of death)

Mangili, submitted 2008

Nutrition in HCV/DU/HIV

- Issues are:
  - Assessment of nutritional status
  - Access to nutrition
  - Appetite
  - Symptoms which may decrease intake
  - Dietary quality
  - Metabolism (what are nutrient requirements in setting of inflammatory infections?)
  - Malabsorption

Predictors of Food Security

(n=592)

	Food secure 37%	Food insecure 63%	P
Age	42 years	40 years	0.01
Female	23%	77%	<0.001
Non-white	19%	81%	<0.001
IDU	**16%**	**84%**	**<0.001**
No ART	34%	66%	0.08
BMI	**25.0 kg/m^2**	**26.4 kg/m^2**	**0.01**
CD4	311	342	0.08
Viral load (log)	3.4	3.5	0.38

McMahon 2011

NFHL Cluster Analysis Results

- Fruits/ Vegetables:
  - Lowest risk of poverty or food insecurity
  - Highest intakes of protein, fiber, and micronutrients
  - Highest levels of LBM and CD4 count
- Fast Food:
  - More likely to live in poverty, be food insecure or IDU
  - Diets of lower nutrient density
  - Highest levels of viral load, lowest mean CD4, most likely to have AIDS diagnosis
- Juice and Soda:
  - Lowest BMI and highest reported mean calorie intake

Hendricks, Am J Clin Nutr 2008.

Top 3 vegetables by study site:

Baltimore (n=123)	Onion, cooked (18%) Potato Chips (14%) French Fries (10%)
Providence (n=110)	Potato Chips (20%) Onion (9%) Iceburg Lettuce (7%)
Boston (n=80)	Vegetable mix, corn and lima beans (7.5%) French Fries (7.5%) Tossed salad (6%)

Potential for Nutrition Interventions

- To attempt to slow steatosis:
  - Weight reduction (decrease BMI)
  - Improve glucose tolerance/ decrease HOMA
- To attempt to slow fibrosis
  - Improve glucose tolerance
  - Reduce alcohol consumption
- To improve treatment response:
  - Treat glucose intolerance/ decrease HOMA

Recommendations

- Monitor weight (with height) in HCV infection
- Monitor glucose and insulin
  - (HOMA= $\frac{\text{fasting insulin x fasting glucose}}{22.5}$
- ? Monitor Hgb A1c
- Monitor lipid profile (TG, TC, LDL, HDL)

Recommendations

- Consider
  - Treatment for elevated HOMA prior to HCV treatment
  - Insulin sensitizing agents
  - No evidence to support success
- Treat lipids if response to treatment increases TC/ LDL to level of CVD risk

Summary

- Nutritional/ Metabolic parameters
  - occur with HCV infection
  - appear to contribute to HCV progression
  - may play a role in response to HCV treatment

Summary

- Lipid abnormalities occur in HCV
- Weight/BMI contribute to outcomes in HCV
- More research is needed on impact of intervention in these abnormalities
- Nutritional or metabolic interventions may offer additional means to effect improvements in quality of care in HCV