Higher Carnitine Levels are Associated with Subsequent Myocardial Infarctions in HIV

Arjun Sinha[1], Yifei Ma[1], Rebecca Scherzer[1], Sophia Hur[1], Danny Li[1], Heidi Crane[2], Daniel Drozd[2], Jeffrey Martin[1], Peter Ganz[1], Steven Deeks[1], Peter Hunt[1], Priscilla Hsue[1]
[1]University of California at San Francisco, CA, USA; [2]University of Washington, Seattle, WA, USA

Background

- HIV-infected adults have 50% increased risk of myocardial infarction (MI) and four-fold higher rates of sudden cardiac death as compared to the general population without HIV.
- HIV preferentially infects CD4+ T-cells in the gut which causes alterations in gut mucosa and microbiota and subsequent downstream chronic inflammation.
- Choline, carnitine, betaine, and trimethylamine N-oxide (TMAO) are gut microbiota associated small molecules that are associated with atherosclerosis and MI in the general population.
- The objective of our study was to investigate the association of these four small molecules with MI in a nested case-control study.

Methods

- **Design:** Nested case-control study of HIV-infected adults with suppressed viral load (VL) on antiretroviral therapy (ART) within the US based 8-site CNICS network.
- **Cases with Type I MI:** Adjudicated and confirmed Type 1 MI from 2001-2012, with plasma collected prior to MI (median 3 months [IQR 1-9]).
- **Controls without MI:** ≤3 matched by incidence density sampling to each case by calendar time, age, gender, race, duration of VL suppression, and CD4 count.
- **Measurements:** Plasma levels of TMAO, betaine, carnitine, and choline were measured using stable isotope dilution liquid chromatography tandem mass spectrometry.
- **Analysis:** Associations between the small molecules and MI were assessed using conditional logistic regression after adjusting for traditional cardiovascular risk factors.

Results

Clinical Characteristics

	MI Cases Median (IQR) N=36	Controls Median (IQR) N=69	P Value
Demographics			
Age (years)	50 (47, 58)	49 (46, 57)	*
Race			
Caucasian	17 (47%)	31 (45%)	
African American	18 (50%)	36 (52%)	*
Other	1 (3%)	2 (3%)	*
Male	28 (78%)	53 (77%)	*
HIV Related Factors			
CD4 Count (cells/mm^3)	536 (348, 688)	616 (420, 839)	*
Months VL <400 c/ml	2.8 (1, 4.7)	2.5 (1.2, 6.6)	*
Cardiovascular Risk Factors			
Hypertension	11 (31%)	21 (30%)	0.77
Diabetes mellitus	2 (6%)	3 (4%)	0.81
Active Smoking	13 (36%)	13 (19%)	0.15
TG (mg/dL)	184 (131, 273)	146 (99, 249)	0.05
LDL (mg/dL)	117 (86, 157)	102 (76, 118)	0.11
HDL (mg/dL)	48 (35, 52)	49 (34, 59)	0.37
TC (mg/dL)	182 (162, 240)	178 (155, 208)	0.19

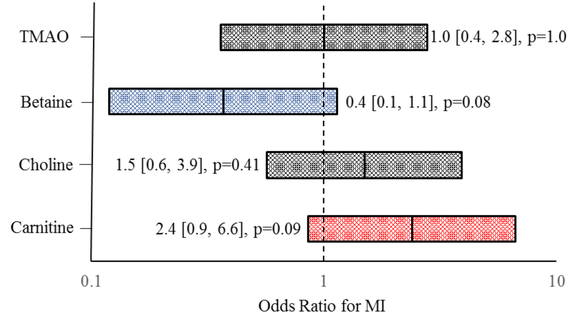
*Matched Variable
p-value for unadjusted OR for association with MI

Serum Levels of the Small Molecules

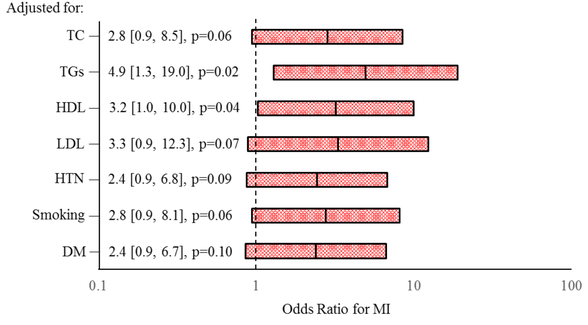
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
TMAO (μM)	< 2.87	2.87 - 3.99	3.99 - 6.1	>6.1
Carnitine (μM)	< 23.82	23.82 - 28.42	28.42 - 33.55	>33.55
Betaine (μM)	< 31.12	31.12 - 35.63	35.63 - 45.35	>45.35
Choline (μM)	< 6.57	6.57 - 7.91	7.91 - 9.45	>9.45

Subjects were divided into quartiles based on the plasma levels of each of the four small molecules to evaluate the association between each small molecule and MI.

Unadjusted OR for MI
Quartile 4 vs Quartiles 1-3

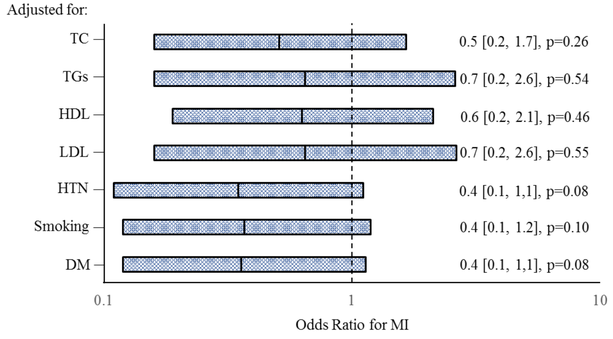


Adjusted OR for MI
Carnitine Quartile 4 vs Quartiles 1-3



After adjusting for triglycerides and HDL, the risk for MI increased and became statistically significant.

Adjusted OR for MI
Betaine Quartile 4 vs Quartiles 1-3



After adjustment, the risk for MI remained low but did not become statistically significant.

Conclusions

- In adults with treated and suppressed HIV, higher carnitine levels were associated with increased risk of MI as compared to individuals with lower levels.
- On the contrary, high betaine levels were associated with decreased risk of MI. We did not observe an association between risk of MI and TMAO or choline.
- Our findings suggest that one potential mechanism of atherosclerosis in the setting of HIV involves carnitine synthesis from betaine.
- Additional studies need to be done to determined whether HIV-associated changes in the gut microbiome and mucosa have an effect on carnitine and betaine serum levels.