Cholesterol Efflux Capacity: Biological and Clinical Determinants in a Large Multi-ethnic Population Study (Dallas Heart Study)

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Background

- Cholesterol efflux capacity (CEC) characterizes the ability of HDL to accept cholesterol from extrahepatic cells in the periphery to the liver, which is a crucial step in reverse cholesterol transport.[1]
- CEC has been shown in clinical studies to be inversely correlated with prevalent coronary disease and incident of cardiovascular events.[1]
- However, It is still unclear what biological determinants or other clinical variables drive cholesterol efflux capacity.

Objective

- To determine the biological and clinical variables that associate with cholesterol efflux capacity measured with two different methods.
- To determine how the measurements of cholesterol efflux capacity and its determinants differ by sex, race, history of diabetes, and history of cardiovascular disease.

Methods

STUDY POPULATION

- Participants of Dallas Heart Study 2 (DHS 2).[2] They are subsets of participants of the DHS 1 who returned for a comprehensive clinical study and repeat data collection between September 2007 and December 2009 (Tables 1&2).

ASSESSMENT OF CHOLESTEROL EFFLUX CAPACITY

- CEC was measured using both fluorescence (Boron Dipyrromethene difluoride-BODIPY) and radiolabeled methods (Figure 1).[3,4]
- CEC was calculated by quantifying the capacity of a participant's plasma depleted of apolipoprotein B to efflux cholesterol from macrophages.

STATISTICAL ANALYSIS

- Variables compared across quartiles of CEC using Jonckheere-Terpstra trend test for continuous variables and Cochran-Armitage trend test for categorical variables.
- CEC measurements compared across sex, race, history of diabetes, and history of cardiovascular disease categories using Mann-Whitney test.
- Variables that were not normally distributed were log transformed for use in the multi-linear regression analysis.
- Multi-linear regression to determine the best predictors of cholesterol efflux capacity.

Results

Table 1. Baseline Demographic and Clinical Characteristics across Quartiles of Cholesterol Efflux Measured by BODIPY Method

Variables	Cholesterol Efflux Capacity				
	Quartile 1 (N = 593)	Quartile 2 (N = 593)	Quartile 3 (N = 594)	Quartile 4 (N = 593)	P Value for Trend
Age (yr)	51 (43-58)	51 (42-59)	50 (41-57)	51 (43-59)	0.95
Male (%)	42.7	42.5	40.4	44.7	0.66
Female (%)	57.3	57.5	59.6	55.3	0.66
Black (%)	54.5	51.9	51.7	45.9	0.005
White (%)	32.2	32.2	32.5	34.6	0.39
Hispanic (%)	11.1	14.2	13.8	17.5	0.003
Hypertension (%)	51.4	54.3	50.7	49.9	0.37
History of CVD (%)	4.9	6.4	5.9	4.0	0.46
Diabetes (%)	15.3	17.5	14.8	18.4	0.35
Current Smoking (%)	22.6	21.5	23.6	21.7	0.93
Systolic Blood Pressure (mmHg)	129 (119-142)	130 (118-144)	130 (117-143)	131 (119-144)	0.994
Body Mass Index (kg/m^2)	30.3 (26.5-36.0)	30.6 (26.3-36.3)	29.8 (26.3-35.0)	30.0 (25.7-34.0)	0.001
Total Cholesterol (mg/dl)	184 (160-211)	185 (160-211)	190 (170-218)	199 (174-224)	<0.001
Triglycerides (mg/dl)	97 (73-133)	102 (72-141)	105 (75-150)	109 (83-163)	<0.001
HDL Cholesterol (mg/dl)	49 (40-58)	49 (42-59)	50 (43-60)	52 (43-62)	<0.001
LDL Cholesterol (mg/dl)	112 (90-134)	110 (89-133)	114 (93-139)	119 (95-140)	0.002
VLDL Cholesterol (mg/dl)	19 (15-27)	20 (14-28)	21 (15-30)	22 (17-33)	<0.001
Non-HDL Cholesterol (mg/dl)	133 (111-160)	131 (109-158)	137 (114-166)	144 (118-171)	<0.001
DEXA Total Percent Fat (%)	39.3 (31.1-46.0)	38.4 (31.3-45.1)	37.7 (30.6-44.6)	37.7 (30.8-44.6)	0.02

Table 2. Baseline Demographic and Clinical Characteristics across Quartiles of Cholesterol Efflux Measured by Radiolabeled Method

Variables	Cholesterol Efflux Capacity				
	Quartile 1 (N = 582)	Quartile 2 (N = 582)	Quartile 3 (N = 582)	Quartile 4 (N = 582)	P Value for Trend
Age (yr)	49 (41-58)	51 (42-58)	50 (43-59)	52 (44-59)	0.001
Male (%)	48.8	41.9	41.9	37.5	<0.001
Female (%)	51.2	58.1	58.1	62.5	<0.001
Black (%)	54.6	52.7	49.8	46.2	0.002
White (%)	29.4	30.2	33.2	38.3	<0.001
Hispanic (%)	13.1	15.1	15.3	14.1	0.62
Hypertension (%)	52.7	50.4	49.7	52.8	0.96
History of CVD (%)	8.1	3.6	4.0	5.0	0.03
Diabetes (%)	16.8	16.3	16.8	16.3	0.88
Current Smoking (%)	21.3	22.4	22.1	24.3	0.27
Systolic Blood Pressure (mmHg)	130 (118-142)	129 (119-143)	130 (119-144)	130 (118-144)	0.74
Body Mass Index (kg/m^2)	30.9 (26.62-37.0)	30.5 (26.9-36.1)	29.7 (26.0-34.5)	28.5 (24.9-33.4)	<0.001
Total Cholesterol (mg/dl)	177 (153-201)	187 (165-210)	193 (173-222)	203 (179-231)	<0.001
Triglycerides (mg/dl)	97 (70-136)	103 (74-144)	105 (76-151)	109 (77-156)	<0.001
HDL Cholesterol (mg/dl)	45 (38-51)	49 (42-57)	52 (44-61)	56 (47-70)	<0.001
LDL Cholesterol (mg/dl)	107 (88-132)	114 (93-136)	115 (94-143)	117 (93-141)	<0.001
VLDL Cholesterol (mg/dl)	19 (14-27)	21 (15-29)	21 (15-30)	22 (15-31)	<0.001
Non-HDL Cholesterol (mg/dl)	131 (108-155)	136 (114-162)	140 (117-168)	142 (116-172)	<0.001
DEXA Total Percent Fat (%)	37.8 (31.0-45.3)	39.0 (31.7-45.6)	37.9 (30.4-45.6)	38.3 (31.0-44.4)	0.35

Continuous variables reported in medians (IQR)

Table 3. Cholesterol Efflux Capacity across Sex-specific, Race-specific, History of CVD, and History of diabetes Categories

	BODIPY		Radiolabeled	
	N	CEC	N	CEC
Sex				
Men	1010	0.82 (0.66-0.99)	990	0.93 (0.81-1.03)
Women	1363	0.82 (0.66-0.98)	1338	0.95 (0.84-1.05)
P value		0.52		<0.001
Race				
Black	1210	0.81(0.64-0.96)	1184	0.93(0.81-1.03)
Other[a]	1163	0.83(0.68-1.00)	1144	0.95(0.83-1.05)
P value		0.006		0.007
History of CVD				
Yes	126	0.81 (0.69-0.95)	120	0.89 (0.78-1.05)
No	2213	0.82 (0.66-0.98)	2175	0.94 (0.83-1.05)
P value		0.59		0.048
History of Diabetes				
Yes	392	0.82 (0.67-0.99)	386	0.94 (0.82-1.05)
No	1981	0.82 (0.65-0.98)	1942	0.94 (0.83-1.05)
P value		0.32		0.81

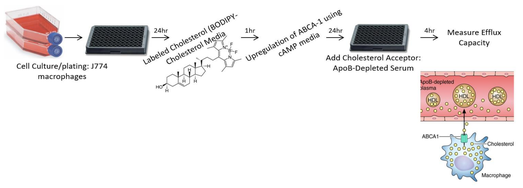
Table 4. Multi-linear Regression Results for Cholesterol Efflux Capacity and Clinical Variables by Method of Measurement

N=2320	CEC (Radiolabeled) Adj R^2=0.195	
Variable	Std β	P Value
HDL Cholesterol	0.442	<0.001
Log Triglyceride	0.281	<0.001
LDL Cholesterol	0.082	<0.001
BMI	-0.056	0.004
N=2335	CEC (BODIPY) Adj R^2=0.099	
Variable	Std β	P Value
Total Cholesterol	0.316	<0.001
Plate Number	0.221	<0.001
Log HOMA IR	0.117	0.08
Log VLDL	0.073	0.01
Non-Hispanic Black	0.029	0.16
Low HDL	-0.072	0.003
Log Insulin	-0.163	0.01
LDL Cholesterol	-0.221	<0.001

Variables are listed in order of magnitude from positive to negative association for each model. Other variables included in the model are age, sex, HTN, CVD, diabetes, stroke, smoking, alcohol use, MET, blood pressure, waist-to-hip ratio, non-HDL cholesterol, hsCRP, CAC, and DEXA total fat mass

Cholesterol Efflux Assay

Figure 1. Cholesterol Efflux Assay



Summary

- Cholesterol efflux capacity measured by radiolabeled method was significantly higher in women than in men, p<0.001 (Table 3).
- Blacks had the lowest cholesterol efflux capacity measured by both BODIDY (p=0.010) and radiolabeled (p<0.001) methods (Table 3).
- Participants without history of CVD had higher cholesterol efflux capacity measured by radiolabeled method compared to those with history of CVD, p=0.048 (Table 3).
- In multivariate regression, risk factors and circulating markers explained more of the variance in efflux using radiolabel than the variance in efflux using BODIPY (R2 0.195 vs. 0.099) with some overlapping and some distinct markers (Table 4). Stratification by history of CVD, history of diabetes, race, and sex categories did not alter the findings.

Conclusion

- Our analysis revealed that biological and clinical variables that associate with cholesterol efflux capacity vary with measurement methods. Further studies with different study population validating these differences are needed.
- An understanding of the differences in the clinical and biological variables that associate with efflux will be useful in identifying targets to improve cholesterol efflux capacity.

References

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