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Carbohydrate restriction-induced elevations in LDL-cholesterol and atherosclerosis:

The KETO Trial

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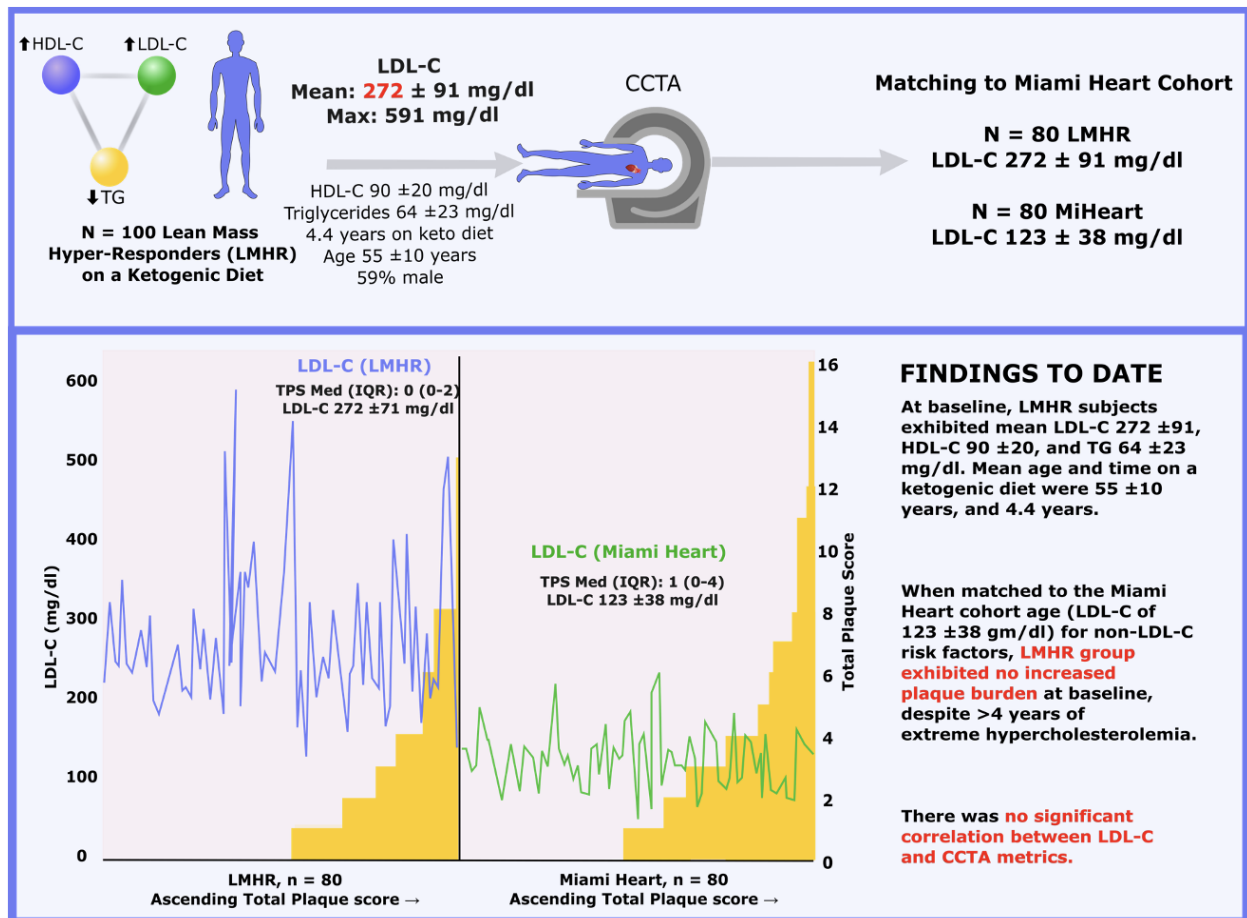[3] Citizen Science Foundation, Las Vegas, Nevada
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NCT05733325	Diet-induced Elevations in LDL-C and Progression of Atherosclerosis (Keto-CTA)

GRAPHICAL ABSTRACT

↑HDL-C   ↑LDL-C

↓TG

N = 100 Lean Mass Hyper-Responders (LMHR) on a Ketogenic Diet

LDL-C Mean: 272 ± 91 mg/dl Max: 591 mg/dl

HDL-C 90 ±20 mg/dl
Triglycerides 64 ±23 mg/dl
4.4 years on keto diet
Age 55 ±10 years
59% male

CCTA

Matching to Miami Heart Cohort

N = 80 LMHR LDL-C 272 ± 91 mg/dl

N = 80 MiHeart LDL-C 123 ± 38 mg/dl

LDL-C (LMHR)
TPS Med (IQR): 0 (0-2)
LDL-C 272 ±71 mg/dl

LDL-C (Miami Heart)
TPS Med (IQR): 1 (0-4)
LDL-C 123 ±38 mg/dl

LDL-C (mg/dl)

Total Plaque Score

LMHR, n = 80
Ascending Total Plaque score →

Miami Heart, n = 80
Ascending Total Plaque score →

FINDINGS TO DATE

At baseline, LMHR subjects exhibited mean LDL-C 272 ±91, HDL-C 90 ±20, and TG 64 ±23 mg/dl. Mean age and time on a ketogenic diet were 55 ±10 years, and 4.4 years.

When matched to the Miami Heart cohort age (LDL-C of 123 ±38 gm/dl) for non-LDL-C risk factors, LMHR group exhibited no increased plaque burden at baseline, despite >4 years of extreme hypercholesterolemia.

There was no significant correlation between LDL-C and CCTA metrics.

Abbreviations: Coronary Artery Calcium (CAC), Coronary CT Angiography (CCTA), LDL-cholesterol (LDL-C), Lean-Mass Hyper-Responder (LMHR), Miami Heart Study (MiHeart), Segment Involvement Score (SIS), Total Plaque Score (TPS), Total Stenosis Score (TSS)

Introduction/Objective:
While most individuals who adopt carbohydrate restricted ketogenic diets for obesity or diabetes exhibit improvements in lipid parameters, some who adopt these diets exhibit increases in LDL-cholesterol (LDL-C). A population of these individuals, termed lean-mass hyper-responders (LMHRs) – previously defined by the metabolic triad of elevations in LDL-C and HDL-C with low triglycerides on a carbohydrate-restricted diet – exhibit extreme increases in LDL-C. It is unknown, in this context of otherwise good metabolic health, whether or to what degree the increases in LDL-C induced by carbohydrate restriction may accelerate atherosclerosis. The aim of this study is to prospectively evaluate the plaque progression over the course of 1-year in 100 metabolically health LMHR subjects on a ketogenic diet with LDL-C ≥190 mg/dl. Herein, we present the baseline characteristics of the cohort and pre-specified analysis of quantitative plaque measures from coronary CT angiography (CCTA) data in the 100 LMHR subjects, with matching to subjects from The Miami Heart Study (MiHeart), a population based study of atherosclerosis with participants undergoing CCTA.

Methods:

80 LMHR or near-LMHR asymptomatic subjects with LDL-C ≥ 190, HDL-C ≥ 60, and triglycerides ≤ 80 mg/dl were matched 1:1 for age, gender, race, diabetes mellitus, hyperlipidemia, hypertension, and past smoking to asymptomatic subjects from the MiHeart cohort. The 20 LMHR subjects not matched were outside the MiHeart cohort age range of 40-65 years. LMHR followed a ketogenic diet (very low carb diet), usually <30g/d, sufficient to induce an elevation in circulating ketone bodies, which was measured and was required to be elevated in these participants to be enrolled. Primary analysis were levels of Coronary Artery Calcium (CAC), Total Plaque Score (TPS), Total Stenosis Score (TSS) and Segment Involvement Score (SIS), analyzed with the Wilcoxon Rank Sum test. All measures were done in the same CT laboratory by expert readers blinded to all clinical variables and diet information.

Results:

The mean age of the LMHR cohort was 55.3 ± 10.3, 59% male, with mean LDL-C of 272 ± 91 mg/dl [max LDL-C 591 mg/dl], matched 1:1 to Miami Heart cohort, with similar age, sex, race/ethnicity and risk factors including systolic, diastolic blood pressures, smoking history, diabetes, hemoglobin A1c (all p>0.05) and LDL-C of 123±38 mg/dl. Mean duration of ketogenesis was 4.7±2.8 years at time of CCTA. There was no significant difference in the LMHR subjects total CAC score (median and IQR)[0 (0,56)] versus in MiHeart[1(0, 49)],p = 0.520 and no significant difference in the CCTA outcomes; TSS[0 (0,3) versus 1(0,3),p=0.357], TPS[0(0,2) versus 1(0,4),p=0.357], and SI[0 (0,2) versus 1(0,3),p=0.366]. Further, there was no significant correlation between LDL-C level and CCTA plaque metrics (Figure 1).

Conclusion:
After a mean duration of 4.7 years of carbohydrate restriction-induced elevations in LDL-cholesterol, a metabolically healthy cohort of subjects on a ketogenic diet did not have greater atherosclerotic burden than participants from a population based cohort with similar risk profiles but markedly lower LDL-C.

Figure 1. Total Plaque Score plotted against LDL-C between 80 LMHR subjects matched 1:1 to 80 Miami Heart (MiHeart) subjects.

LDL-C versus Total Plaque Score

LMHR
TPS Med (IQR): 0 (0-2)
LDL-C: 272 ± 91 mg/dl

LDL-C ——
TPS ▮

LMHR
TPS Med (IQR): 0 (0-2)
LDL-C: 272 ± 91

MiHeart
TPS Med (IQR): 1 (0-4)
LDL-C: 123 ± 38 mg/dl

LDL-C mg/dl

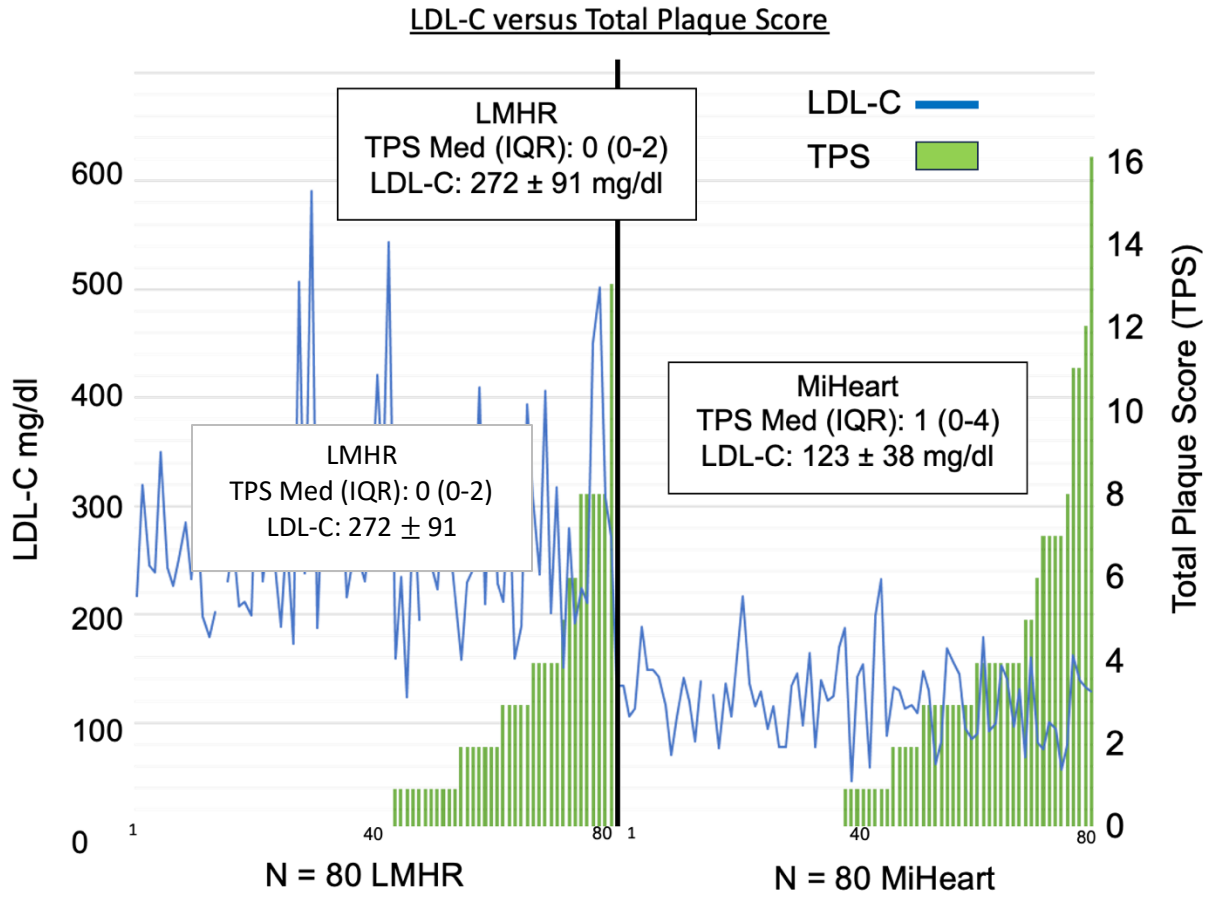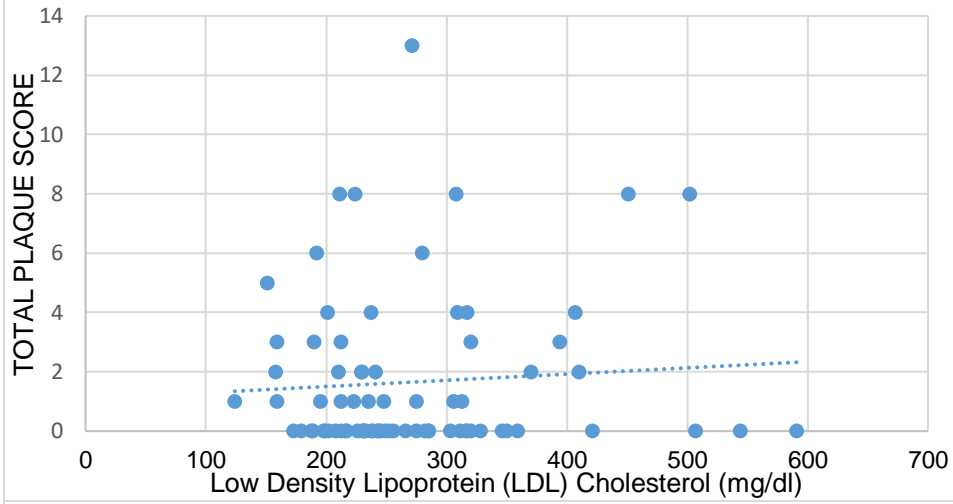Total Plaque Score (TPS)

N = 80 LMHR

N = 80 MiHeart

Figure 2. Total Plaque Score plotted against LDL-C, including between LMHR subjects (top) matched 1:1 to 80 Miami Heart (MiHeart) subjects (bottom).

Lean Mass Hyper Responders

TOTAL PLAQUE SCORE vs. Low Density Lipoprotein (LDL) Cholesterol (mg/dl)

MiHeart Matched Cohort

TOTAL PLAQUE SCORE vs. LDL-Cholesterol (mg/dl)