Genetics Outline

# Background

* Clinical Question
* Role of Diet vs Genetics
* Individual responses to KD vary in terms of cholesterol
* Potential cholesterol response scenarios: hyper- vs non-hypercholesterolemic

# Methods

Reviewed data from the Choi et al meta-analysis (http://dx.doi.org/10.3390/nu12072005), pulling in data on baseline weight, weight changes, LDL, LDL changes and standard deviations. A systematic literature search of PubMed was then performed to identify other randomized controlled trials (RCTs) and single-arm interventions of patients that evaluated the effects of a ketogenic diet on weight and lipid profile as primary endpoints. All studies using a KD diet that met our inclusion criteria where intake of carbohydrate was less than 25 grams per day were included. This search was most recently updated on Thu May 05 14:20:22 2022.

We used a value 130mg/dL of LDL-C at baseline to stratify individuals as being hypercholesterolemic or not.

Correlations in this meta-analysis before and after the administration of the ketogenic diet were analyzed with linear models and results given using pearsons correlation coefficient, statistical significance was defined as below 0.05.

For all outcomes, we tested sex as a modifier and as a covariate. For outcomes where sex was found to be a significant modifier, these results are reported.

# Human Section

## Across Ketogenic Diet Studies, Baseline LDL is not Associated with Increases in LDL

* A LDL vs delta LDL
  + Studies with more weight loss have lower increases in LDL
  + Change in LDL on KD has no positive correlation with Baseline LDL
* B BMI vs delta LDL **update to BMI**

We evaluated 19 studies for this meta-analysis. Using the meta-analysis method, we found fasting blood LDL-C levels were increased 11.474 mg/dL (95% CI: 1.112 to 21.836) after the ketogenic diet intervention compared to pre-intervention levels, with a significant p-value of 0.03. Across these studies, the I2 is 0, the p-value for Q is 0.997. This is a highly consistent I^2.

Lower baseline BMI was associated with an increased change in LDL-C after consumption of a ketogenic diet (r2 = 0.538, p-value = 0.004). The association with increased LDL-C was consistent with baseline weight, where a lower baseline weight was associated with an increased change in LDL-C (r2 = 0.478, p-value = 0.001).

Greater BMI decreases over the study period were associated with a smaller increase in LDL-C after consumption of a ketogenic diet, though this did not reach significance (r2 = 0.315, p-value = 0.072). The association with the change in LDL-C and decrease in BMI was consistent with weight, with change in weight on LDL-C reaching significance (r2 = 0.216, p-value = 0.045), where greater decreases in weight were associated with lower increases in LDL-C after consumption of a ketogenic diet. Looking at percent BMI change to account for baseline BMI, greater percent change decreases were associated with a lower increase in LDL-C on a ketogenic diet, though this was not significant (r2 = 0.274, p-value = 0.098).

Among individuals, baseline LDL-C was not positively correlated with change in LDL-C after consumption of a ketogenic diet and the relationship was not significant (r2 = 0.1, p-value = 0.152).

## There is a Weak Negative Relationship between Baseline LDL-C and Change in LDL-C on a Ketogenic Diet

* A LDL-C
* B Pct Change in LDL-C
* C Hypercholest
* D BMI

Suppelementary Figure Sex Differences, Study Differences

* Comparison of studies (supplement)
* Relationships between:
  + BMI and LDL
  + Weight change and LDL (supplement)
  + Baseline and change in LDL
  + Baseline and percent change in LDL
  + Effects of gender (supplement)
* Stratified by hypercholesterolemia status
  + Change in LDL
* Statin use analysis (supplement)

# Mouse Section

## SNPs Associated with Cholesterol Levels on NCD are distinct from Associated SNPs on HFHS Diet

* SNPs associated with cholesterol on NCD
  + Lead SNP
* SNPs associated with cholesterol on HFD
  + Previous lead SNP
* Polygenic risk scores
  + Predict NCD but not HFD cholesterol

## Liver Gene Expression Associations with Cholesterol on NCD are Unique Relative to HFHS Diet

* Liver gene expression associations with cholesterol on NCD
  + Fbp1
* Unique liver gene expressions associated with cholesterol on HFD
  + Fbp1 no longer has the same cholesterol associations
* Inbred strains on HFD vs chow (supplement?)

# Conclusions

* No positive relationship between baseline LDL and change in LDL
* In mice, genetics predicting LDL is independent of diet-induced changes in LDL