Are low-fat diets good for everyone? Effects of dietary intake on LDL subclass phenotype and risk of coronary heart disease

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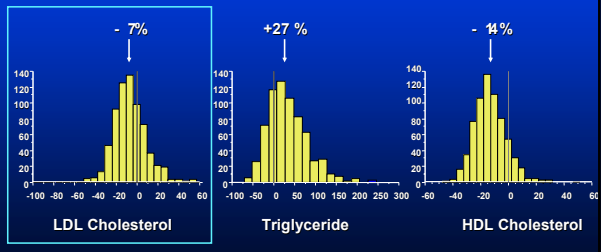
Assumptions Underlying Low-Fat Dietary Recommendations

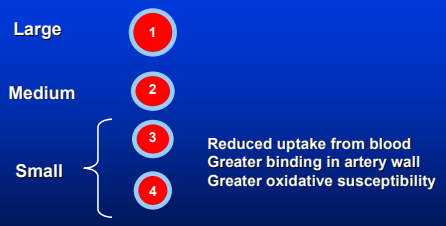
- Individuals on low-fat diets are more likely to consume less saturated fat, which in turn can lead to lower LDL cholesterol
- Fat is calorie-dense, hence lower fat diets will lead to less calorie intake and weight loss
- The population as a whole can benefit from reducing dietary fat
- Substituting carbohydrates for fats is healthier

There are a range of lipid and lipoprotein responses to low-fat diets

Genetics of Lipoproteins and Diet (GOLD)
688 men and women; 20-24 % vs. 40-46% fat, 4-6 weeks,

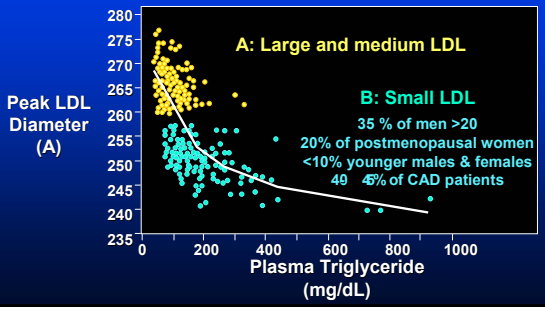


LDL Consists of Multiple Discrete Subclasses



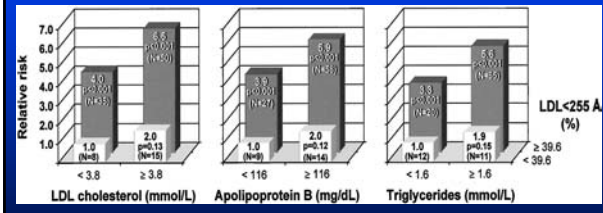
Distribution of subclasses
is independent of total LDL cholesterol

Distinct LDL subclass phenotypes are distinguished by diameter of major LDL species and plasma triglyceride levels



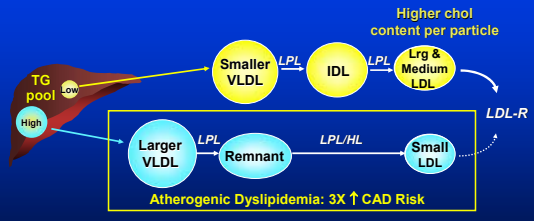
Levels of small LDL are independently predictive of CAD risk

Quebec Cardiovascular Study



St. Pierre et al., Circulation 104:2295, 2001

Model for Origins of LDL Subclasses and Atherogenic Dyslipidemia of Obesity



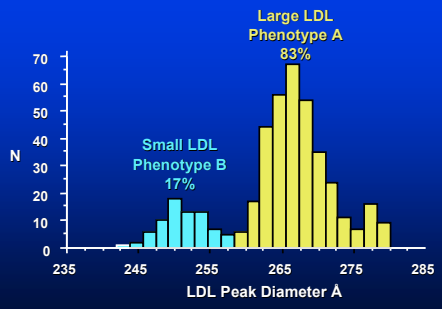
Associated with obesity and insulin resistance

Adapted from Berneis and Krauss, J Lipid Res 43:1155, 2002

Determinants of LDL Subclass Phenotypes

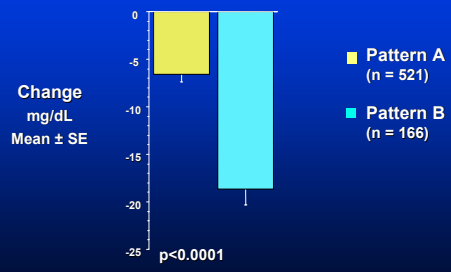
- Heritability ~ 40-75%
- Modifying factors
  - age, gender
  - adiposity/insulin resistance
  - diet ?

LDL Subclass Phenotypes in Healthy Men



Does LDL response to low-fat diet differ between phenotypes?

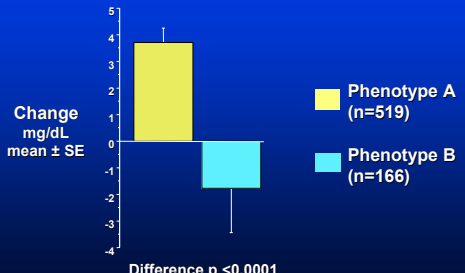
Changes in LDL-Cholesterol Low-Fat (20-24%) vs. High-Fat (40-46%)



Dreon et al. FASEB Journal, 8:121, 1994

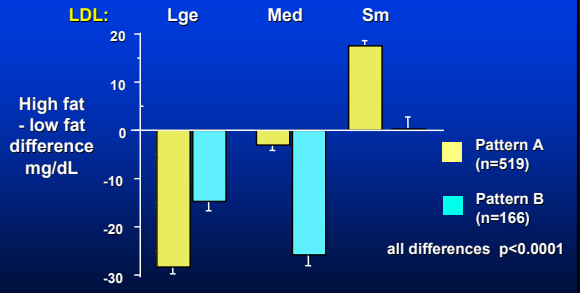
Change in Apoprotein B with Low-Fat Diet

One ApoB molecule/LDL particle;
ApoB is an index of number of particles



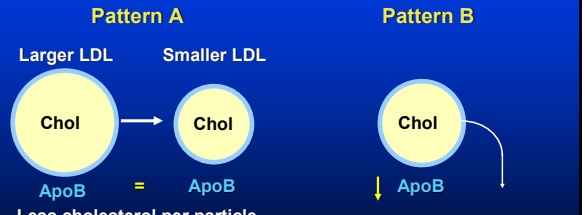
Difference p <0.0001

Changes in LDL Subclasses with Low-Fat High-Carbohydrate Diet



Krauss and Dreon Am. J. Clin. Nutr., 62:478S, 1995

Differing Mechanisms for Reduction in LDL Cholesterol in LDL Pattern A and B

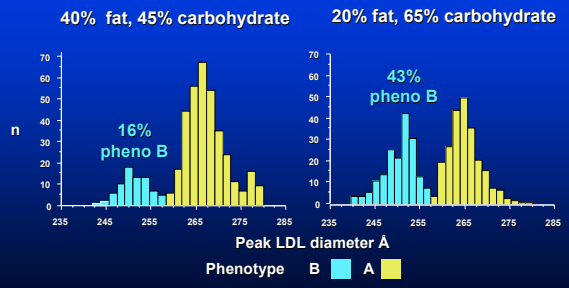


Less cholesterol per particle
Similar number of particles

Reduced number of particles

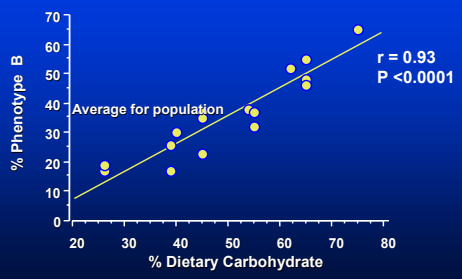
Krauss, Ann Rev Nutr 21:283, 2001

Low-fat, high carbohydrate diet can induce expression of phenotype B



Prevalence of LDL Subclass Phenotype B is Related to Percent Dietary Carbohydrate

Data from 6 studies in healthy men (n = 768)

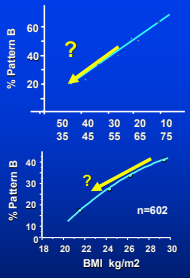


Updated from Dreon et al., AJCN, 1999

Summary (1)

- Individuals with LDL phenotype B, a high-risk heritable trait characterized by a predominance of small dense LDL, show greatest LDL reduction on diets low in total and saturated fat - this subgroup may account for much of the LDL reduction attributable to such diets.
- The LDL reduction with low fat in phenotype B subjects is restricted to less atherogenic medium and larger LDL.
- A high proportion of healthy individuals are predisposed to induction of phenotype B with high carbohydrate-low fat diets.

- Can low carbohydrate intake reverse genetic predisposition to phenotype B?
- Can weight loss also reverse phenotype B, and if so is this independent of dietary fat/carbohydrate?



- Do carbohydrate limitation and/or weight loss attenuate lipoprotein response to saturated fat intake?

Study Design

Subjects: 178 healthy men with BMI 26-35 (mean 29)

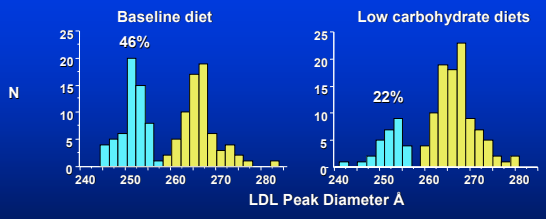
Baseline diet 1 wk: 54% carb, 30% fat, 16% prot (ATP III)

Randomization

	Basal (Control)	Moderate Carbohydrate	Lower Carbohydrate Higher Saturated fat	Lower Carbohydrate Lower Saturated fat
Pre wt loss 3 wk	54% carb 30% fat: 7%Sat 13%Mon 16% prot	39% carb 31% fat: 8%Sat 13%Mon 29% prot	26% carb 45% fat: 15%Sat 20%Mon 29% prot	26% carb 46% fat: 9%Sat 27%Mon 29% prot
Weight loss 1 kg/wk, 5 wk				
Post wt Loss 4 wk				
n	49	42	40	47

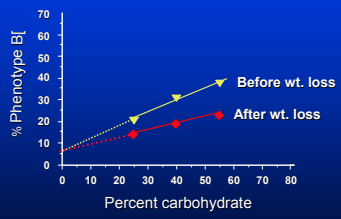
Low Carbohydrate Diets Reverse Phenotype B

129 overweight/obese men randomized to 39% and 26% carbohydrate



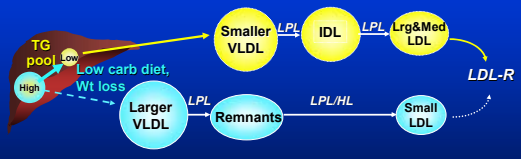
LDL pattern: B A

Prevalence of LDL Phenotype B as a Function of Dietary Carbohydrate Before and After Weight Loss

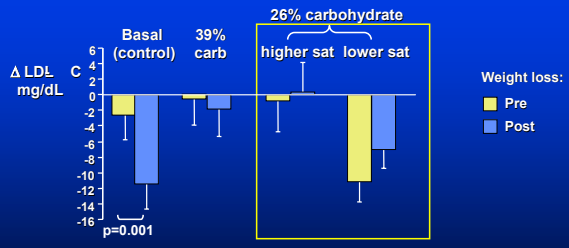


Krauss et al., 2004

Atherogenic lipoprotein phenotype B can be reversed by either reduced dietary carbohydrate or weight loss



Changes in LDL Cholesterol from Baseline



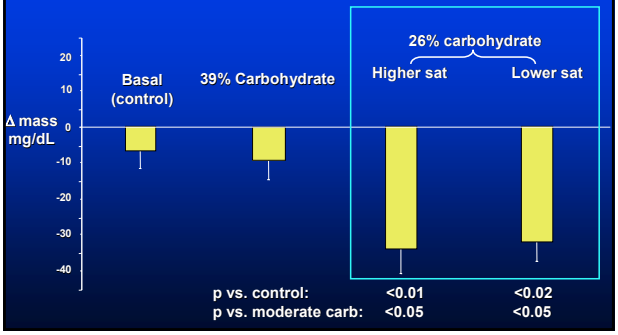
How do these effects compare with those predicted on higher carbohydrate diets?

Apparent Benefits of Reduced Dietary Carbohydrate and/or Increased Protein on LDL-C Response to Dietary Fat

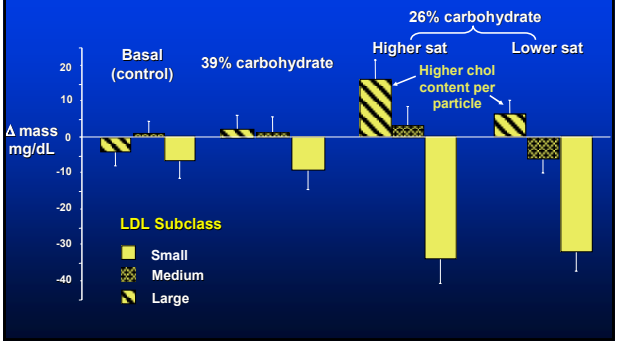
	Changes in LDL-C (mg/dL)	
	Predicted*	Observed
Higher saturated fat	+9	+1
Lower saturated fat	-1	-11

* Mensink et al. AJCN 77:1146, 2003

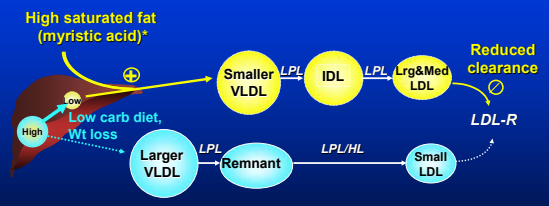
Small LDL levels are reduced by lower carbohydrate intake independent of saturated fat



Higher saturated fat intake raises levels of larger LDL

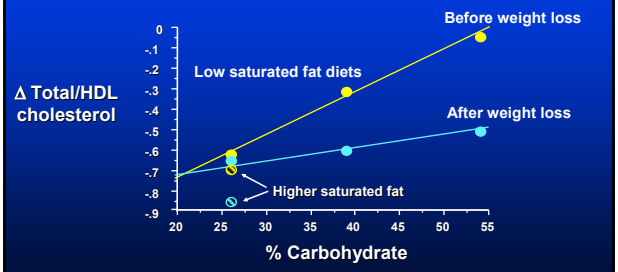


How do dietary carbohydrate and saturated fat affect LDL?



*Kummrow et al J. Lipid Res. 43:2155,2003

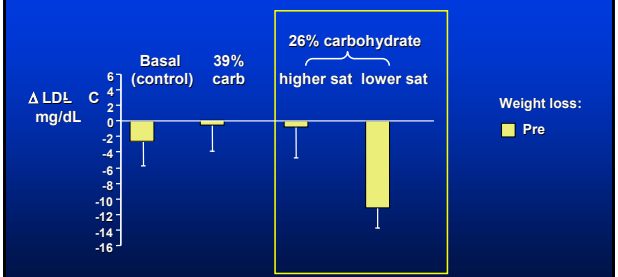
Changes in Total/HDL Cholesterol with Carbohydrate Reduction and Weight Loss



Summary (2)
Effects of Reduced Carbohydrate and Weight Loss on LDL Particles

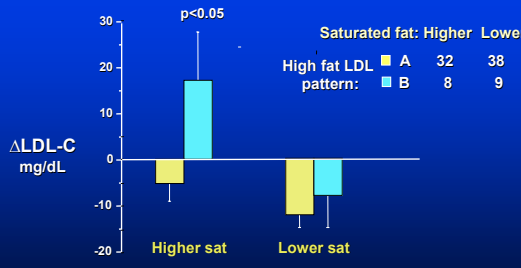
- LDL cholesterol levels on a low carbohydrate, high protein diet are lower than predicted from fat content and composition.
- This is primarily due to reductions in small, dense LDL particles.
- These reductions are independent of dietary saturated fat vs. monounsaturated fat content.
- Weight loss benefits LDL and other atherogenic lipoprotein measures, but these effects are only significant with higher carbohydrate intake.

Changes in LDL Cholesterol from Baseline



Do changes differ in phenotype B vs. A?

Increase in LDL-C with high saturated fat, low carbohydrate diet is restricted to phenotype B subjects



Implications of Findings for Dietary Recommendations

- Moderate weight loss can substantially improve the atherogenic dyslipidemia of obesity and metabolic syndrome.
- Lower carbohydrate intake can achieve similar benefits and is particularly advisable if adequate weight loss is not achieved.
- Limitation of saturated fat intake is not required to improve atherogenic lipid indices in the setting of a lower carbohydrate diet (but some individuals are genetically predisposed to adverse effects of saturated fat).

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Changes in Small LDL with Reduced Dietary Carbohydrate Are Correlated with Changes in Triglyceride