

**CONTROLLING HEART DISEASE
WITH THE ALTERNATE METABOLIC
PATHWAY NUTRITIONAL APPROACH**

Robert C. Atkins, M.D.

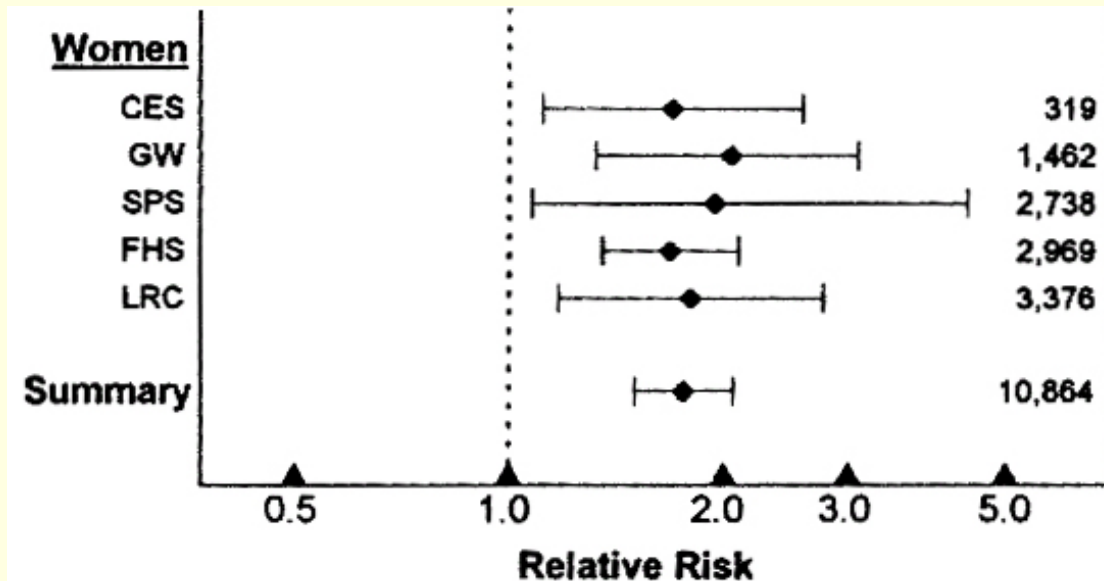
The Atkins Center for Complementary Medicine Cardiology Work-up

- Lipid profile
- Homocysteine
- Lp(a)
- C-reactive protein
- Fibrinogen
- Glucose/insulin studies
- Plus: Stress ECHO, ultrafast CT scan and other non-invasive diagnostic tests

The Nutritional Approach to Heart Disease

- Identify each individual's risk factors.
- Emphasize those most likely for heart disease.
- Select eating regimen to normalize risk factors.
- Select corrective vitanutrients for abnormal findings.
- Reduce dosage of prescribed drugs.
- After 4-6 week trial, then institute pharmacotherapies.

Meta-Analysis of 5 Population-Based Prospective Studies of Triglycerides and Cardiovascular Disease

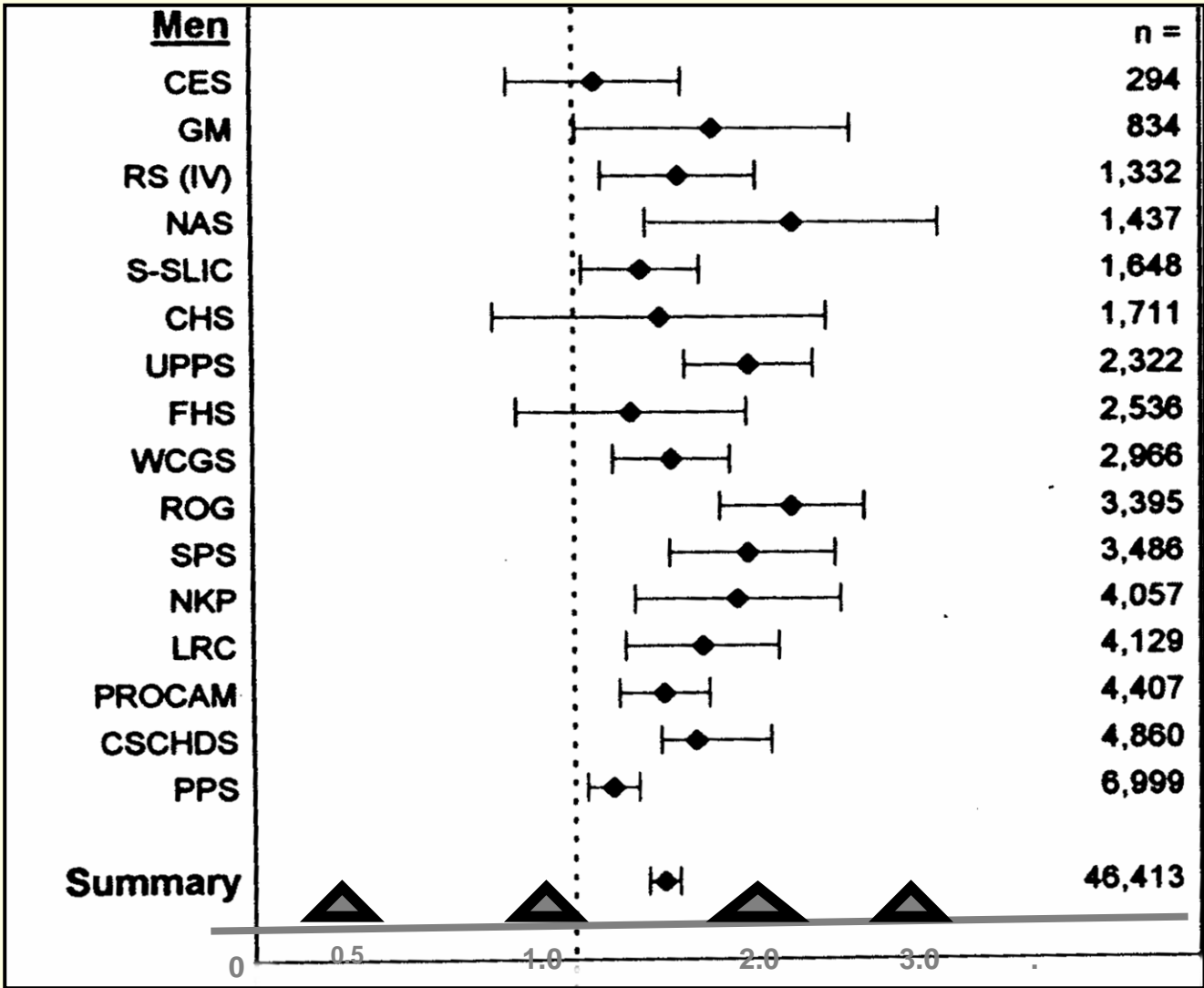


10,864 females followed for 11.4 years totaling 439 events

FIGURE 1. Univariate relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between incident cardiovascular disease and a 1-mmol/L increase in triglyceride, by gender. RR values are given on the x axis on a natural logarithm scale. The y axis lists each study included in the meta-analysis, ordered by sample size, and the summary RR. An RR of 1.0 (vertical dotted line) represents no association, and CIs that do not cover 1.0 indicate RRs that are statistically significant at the $p = 0.05$ level. CHS = Cardiovascular Health Center²; LRC = Lipid Research Clinics Follow-up Study⁵; WCGS = Western Collaborative Health Study^{8,9}; SPS = Stockholm Prospective Study¹⁰; GM = Men Born in 1913 Study¹¹; S-SLIC = Suomi-Salama Life Insurance Cohort¹²; PPS = Paris Prospective Study¹³; GW = Study of Women in Göteborg¹⁴; UPPS = Uppsala Primary Preventive Study¹⁵; FHS = Framingham Heart Study¹⁶; NKP = North Karelia Project¹⁷; CES = Cardiovascular Epidemiology Study¹⁸; NAS = Normative Aging Study¹⁹; CSCHDS = Caerphilly and Speedwell Collaborative Heart Disease Studies²⁰; RS(IV) = Reykjavik Study, Stage IV²¹; PROCAM = Prospective Cardiovascular Munster Study²²; and ROG = Rome Occupational Groups.^{23,24} (Adapted from *J Cardiovasc Risk*.⁶)

Austin, M.A., Hokanson, J.E., Edwards, K.L., "Hypertriglyceridemia as a Cardiovascular Risk Factor," *The American Journal of Cardiology*, 81(4A), 1998, pages 7B-12B.

Meta-Analysis of 16 Population-Based Prospective Studies of Triglycerides and Cardiovascular Disease

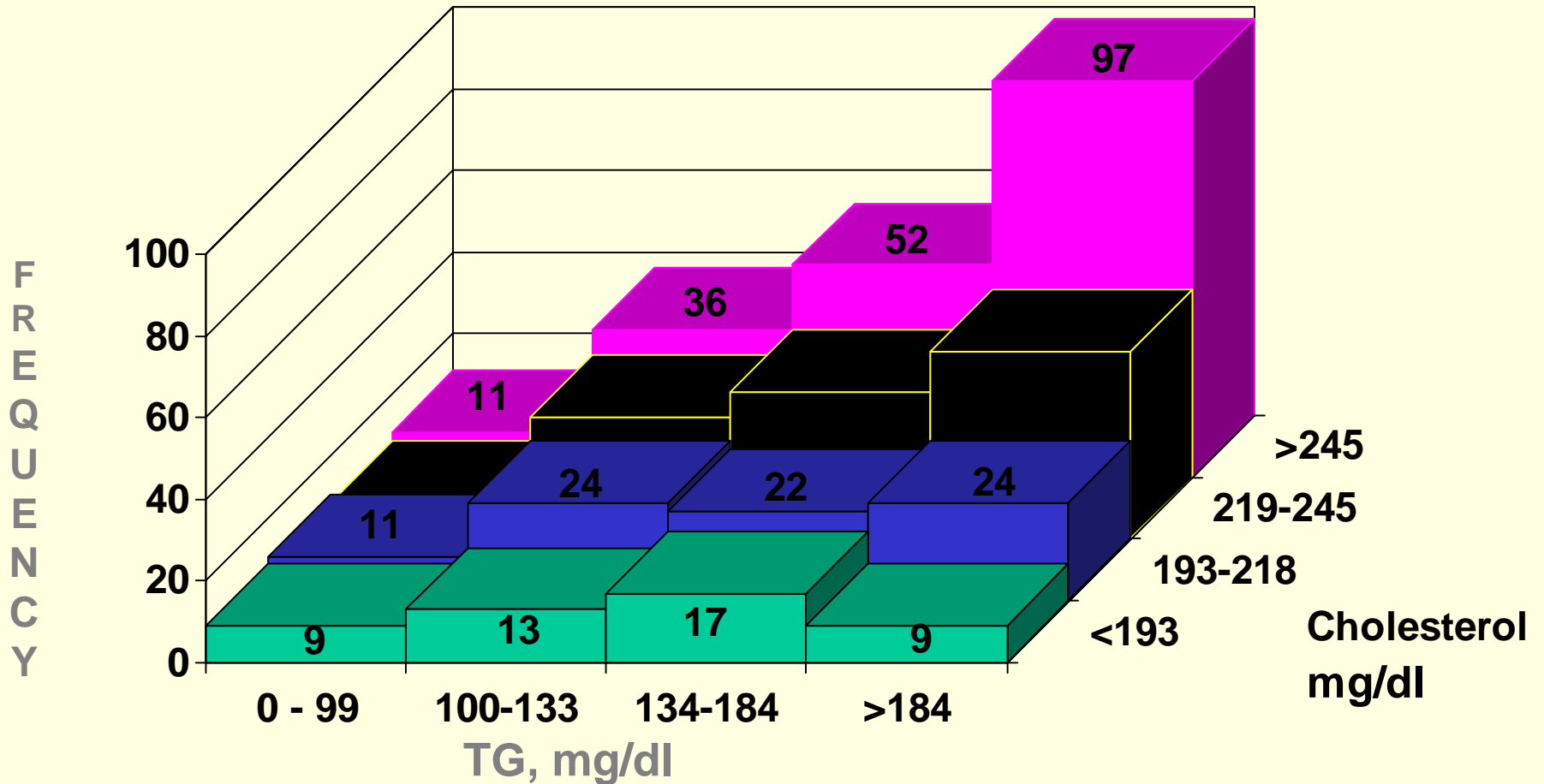


46,413 males followed for 8.4 years totaling 2,445 events

Austin, M.A., Hokanson, J.E., Edwards, K.L., "Hypertriglyceridemia as a Cardiovascular Risk Factor," *The American Journal of Cardiology*, 81(4A), 1998, pages 7B-12B.

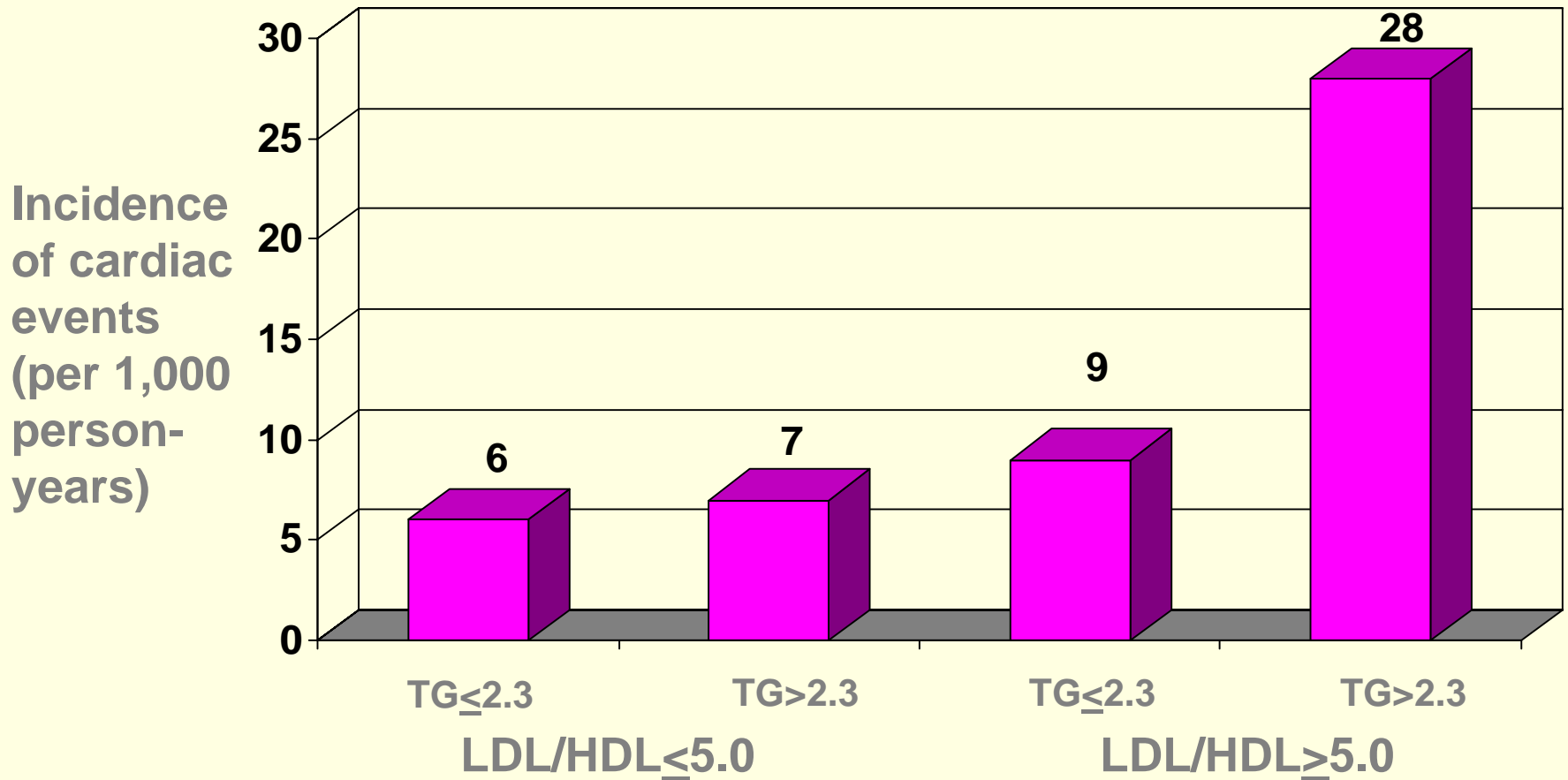
Frequency of Heart Attacks by Cholesterol and Triglyceride (TG)

Strong Interaction Between Cholesterol and TG on the Risk for Heart Attack



Stavenow, L., Kjellström, T., "Influence of Serum Triglyceride Levels on the Risk for Myocardial Infarction in 12,510 Middle Aged Males: Interaction With Serum Cholesterol," *Atherosclerosis*, 147, 1999, pages 243-247.

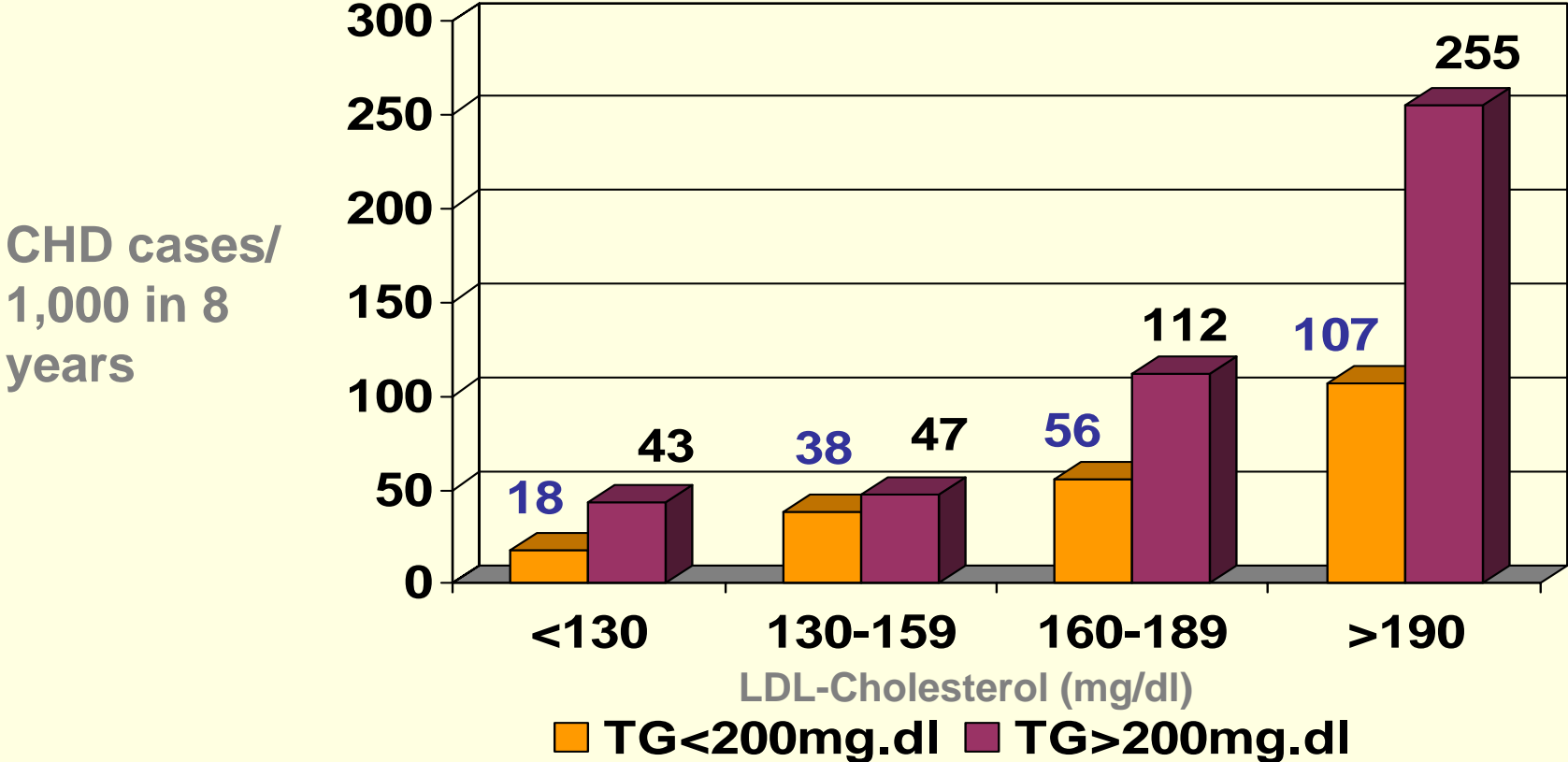
Effect of Triglycerides (TG) and LDL-Cholesterol/HDL-Cholesterol on Coronary Heart Disease



Manninen, V., Tenkanen, L., Koskinen, P., et al., "Joint Effects of Serum Triglyceride and LDL Cholesterol and HDL Cholesterol Concentrations on Coronary Heart Disease Risk in the Helsinki Heart Study: Implications for Treatment," *Circulation*, 85, 1992, pages 37-45.

Incidence of Coronary Heart Disease (CHD)

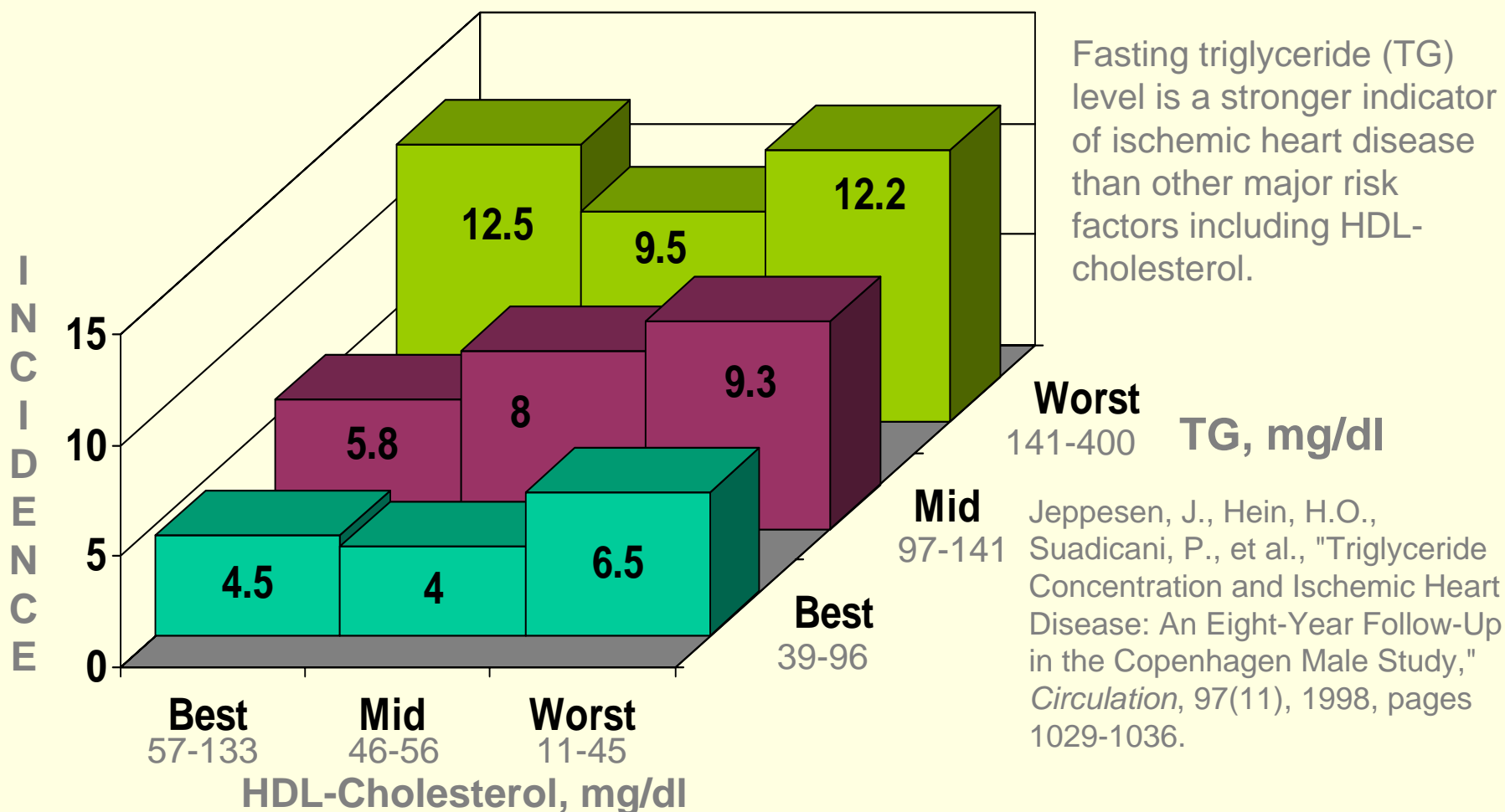
Events According to Serum LDL-Cholesterol and Triglycerides (TG) Concentrations



Assman, G., Schulte, H., Funke, H., et al., "The Emergence of Triglycerides as a Significant Independent Risk Factor in Coronary Artery Disease," *European Heart Journal*, 19(Supplement M), 1998, pages M8-M14.

The Copenhagen Male Study

2,906 Men Without Heart Disease: An 8-Year Follow-up Study



Relative Risk of Heart Attack

Quartile of Log Triglyceride Level/HDL Level

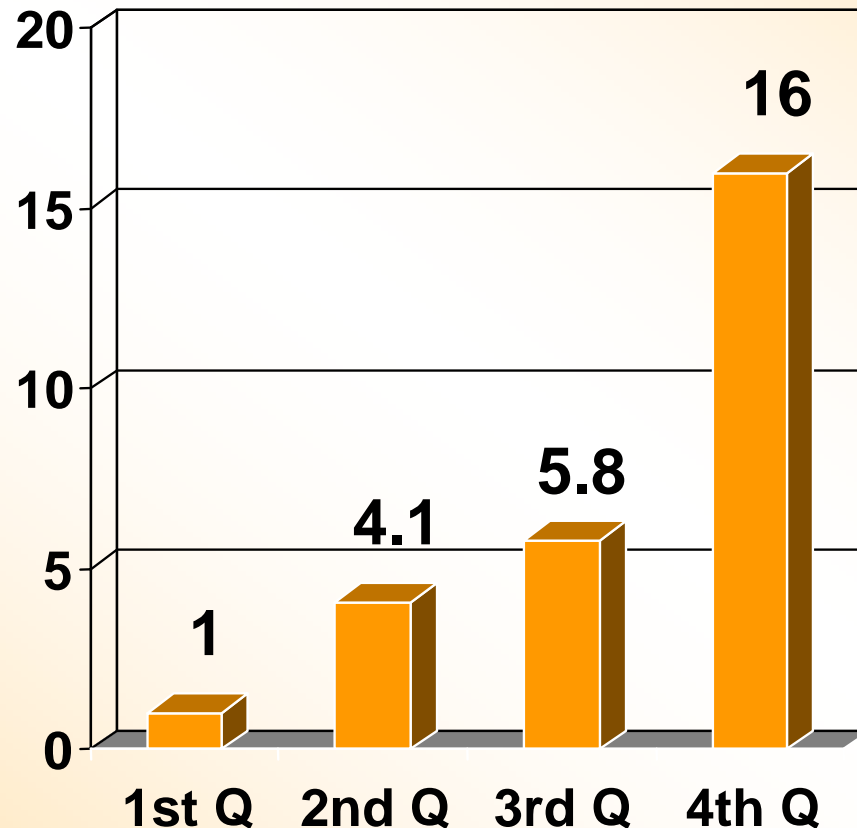
Mean Triglyceride Levels

1st Q=70.1

2nd Q=108.5

3rd Q=138.7

4th Q=278.9



■ Relative Risk

Gaziano, J.M., Hennekens, C.H., O'Donnell, C.J., et al., "Fasting Triglycerides, High-Density Lipoprotein, and Risk of Myocardial Infarction," *Circulation*, 96(8), 1997, pages 2520-2525.

Quintiles of Dietary Glycemic Load (Women)

Quintile	1	2	3	4	5
Quintile mean glycemic load	117	145	161	177	206
Carbohydrate gm/day	144 ± 20	171 ± 11	186 ± 11	200 ± 11	226 ± 20
#CHD Cases	139	128	148	160	186

10-Year Prospective Study: n=75,521 Women

Test for Interaction, P<.0001

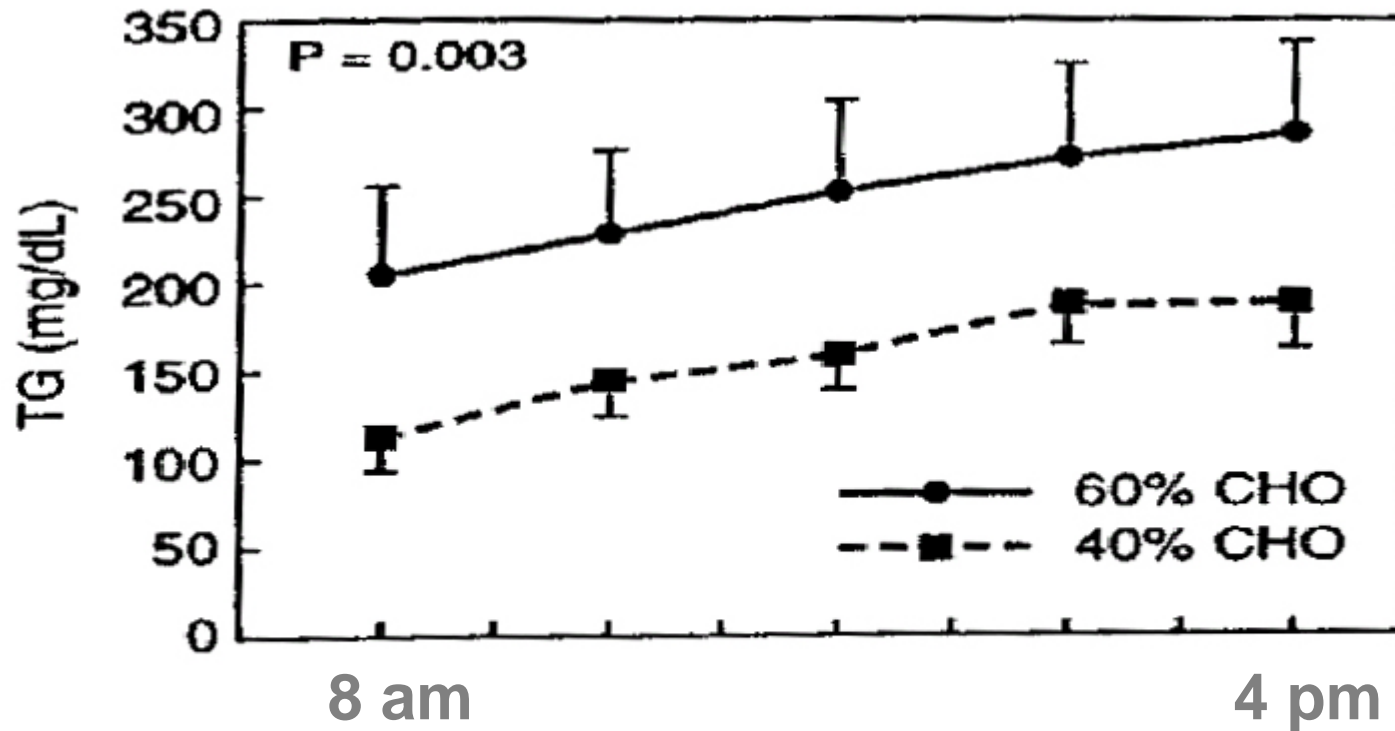
Liu, S., Willett, W.C., Stampfer, M.J., et al., "A Prospective Study of Dietary Glycemic Load, Carbohydrate Intake, and Risk of Coronary Heart Disease in US Women," *The American Journal of Clinical Nutrition*, 71, 2000, pages 1455-1461.

Harvard Nurses Health Study: Summary

“Our findings suggest that a high intake of rapidly digested and absorbed carbohydrate increases the risk of CHD independent of conventional coronary disease risk factors. These data add to the concern that the current low-fat, high-carbohydrate diet recommended in the United States may not be optimal for the prevention of CHD and could actually increase the risk in individuals with high degrees of insulin resistance and glucose intolerance.”

Liu, S., Willett, W.C., Stampfer, M.J., et al., "A Prospective Study of Dietary Glycemic Load, Carbohydrate Intake, and Risk of Coronary Heart Disease in US Women," *The American Journal of Clinical Nutrition*, 71, 2000, pages 1455-1461.

High-Carbohydrate Diet's Effect on Triglycerides (TG)

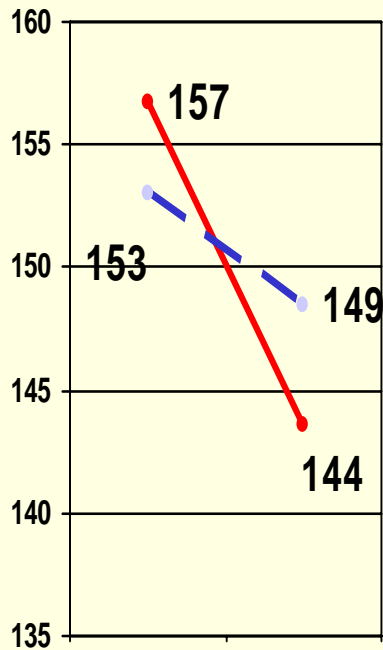


2-week crossover; measured fasting and hourly TG levels from 8 AM - 4 PM.

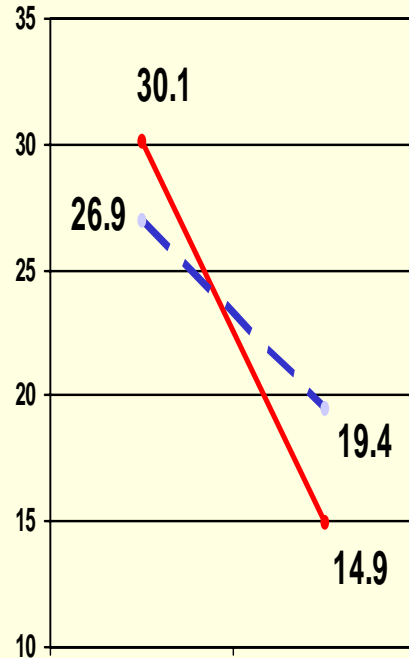
Abbasi, F., McLaughlin, T., Lamendola, C., et al., "High Carbohydrate Diets, Triglyceride-Rich Lipoproteins, and Coronary Heart Disease Risk," *The American Journal of Cardiology*, 85, 2000, pages 45-48.

Serum Lipid Changes: High vs. Moderate Carbohydrate Diets

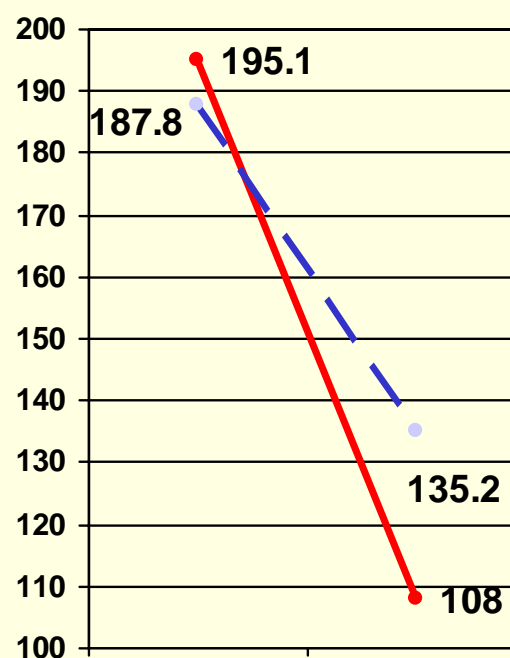
Cholesterol



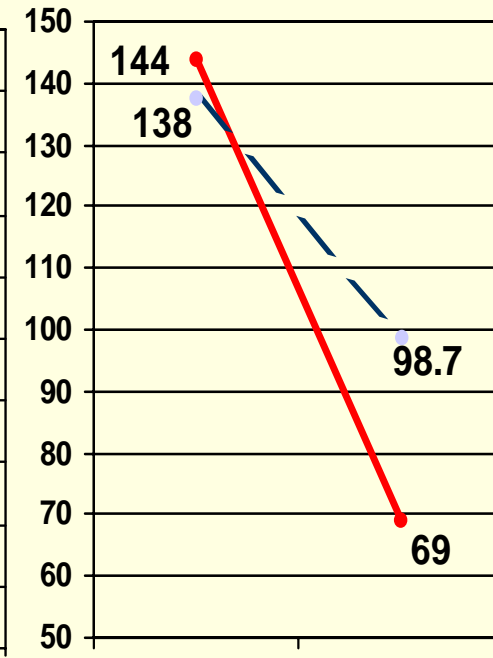
VLDL-Cholesterol



Triglycerides



VLDL-Triglycerides



10 males, 14 days on each 10cals/kg diet

—●— 40% Carbohydrate
—●— 70% Carbohydrate

Lewis, S.B., Wallin, J.D., Kane, J.P., et al., "Effect of Diet Composition on Metabolic Adaptations to Hypocaloric Nutrition: Comparison of High Carbohydrate and High Fat Isocaloric Diets," *The American Journal of Clinical Nutrition*, 30(2), 1977, pages 160-170.

Conclusion From Oakland Naval Study

“Since greater ketonemia was found in the high fat-low-carbohydrate diet in association with similar circulating FFA levels, as in the high carbohydrate-low fat diet, a switch in the intrahepatic metabolism of FFA away from triglyceride synthesis and toward ketone body production could explain both the lowered serum triglyceride levels and higher ketone body levels.” (Note: FFA = free fatty acid)

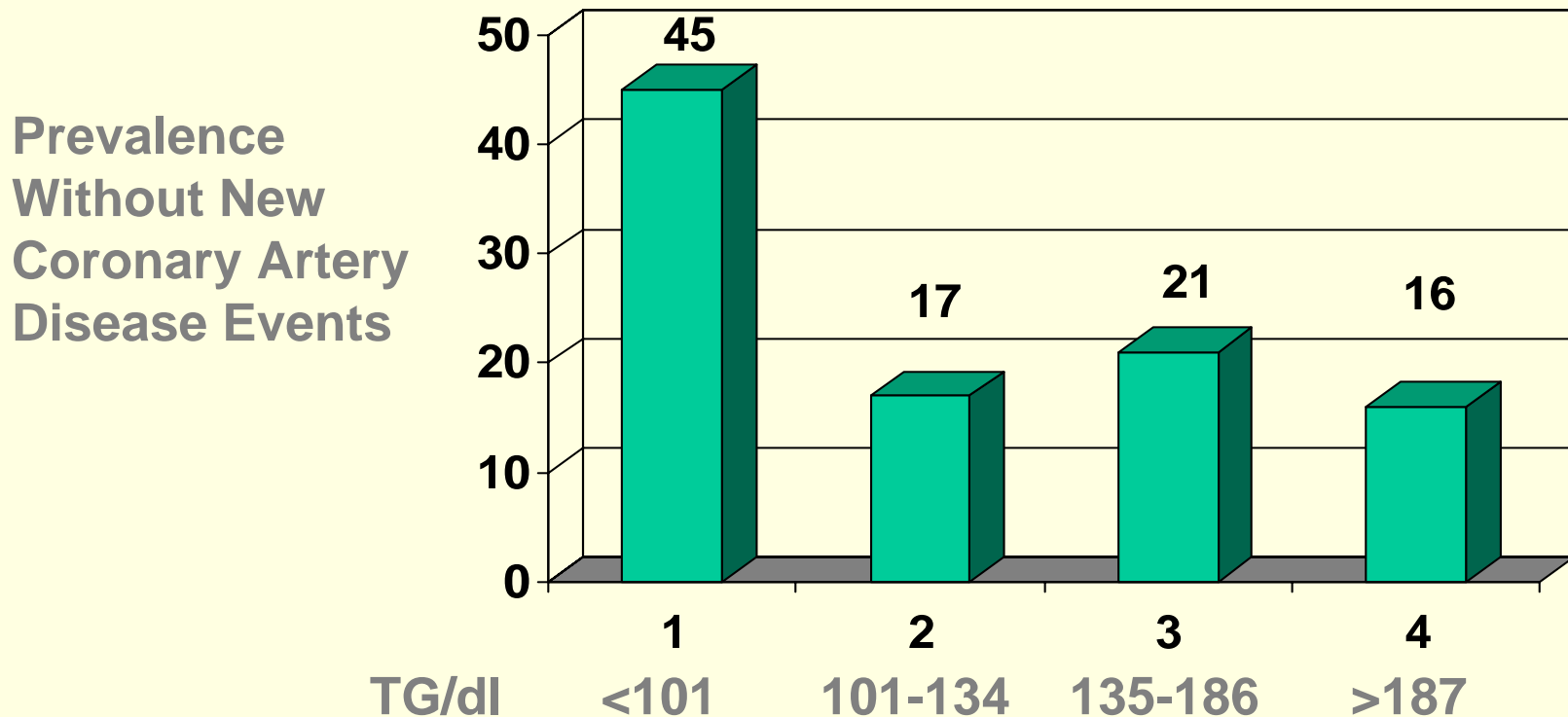
Ketonemia signifies fat is being used as fuel.

Triglyceridemia signifies fat is being stored.

Lewis, S.B., Wallin, J.D., Kane, J.P., et al., "Effect of Diet Composition on Metabolic Adaptations to Hypocaloric Nutrition: Comparison of High Carbohydrate and High Fat Isocaloric Diets," *The American Journal of Clinical Nutrition*, 30(2), 1977, pages 160-170.

Low Triglycerides Protect Against Heart Disease

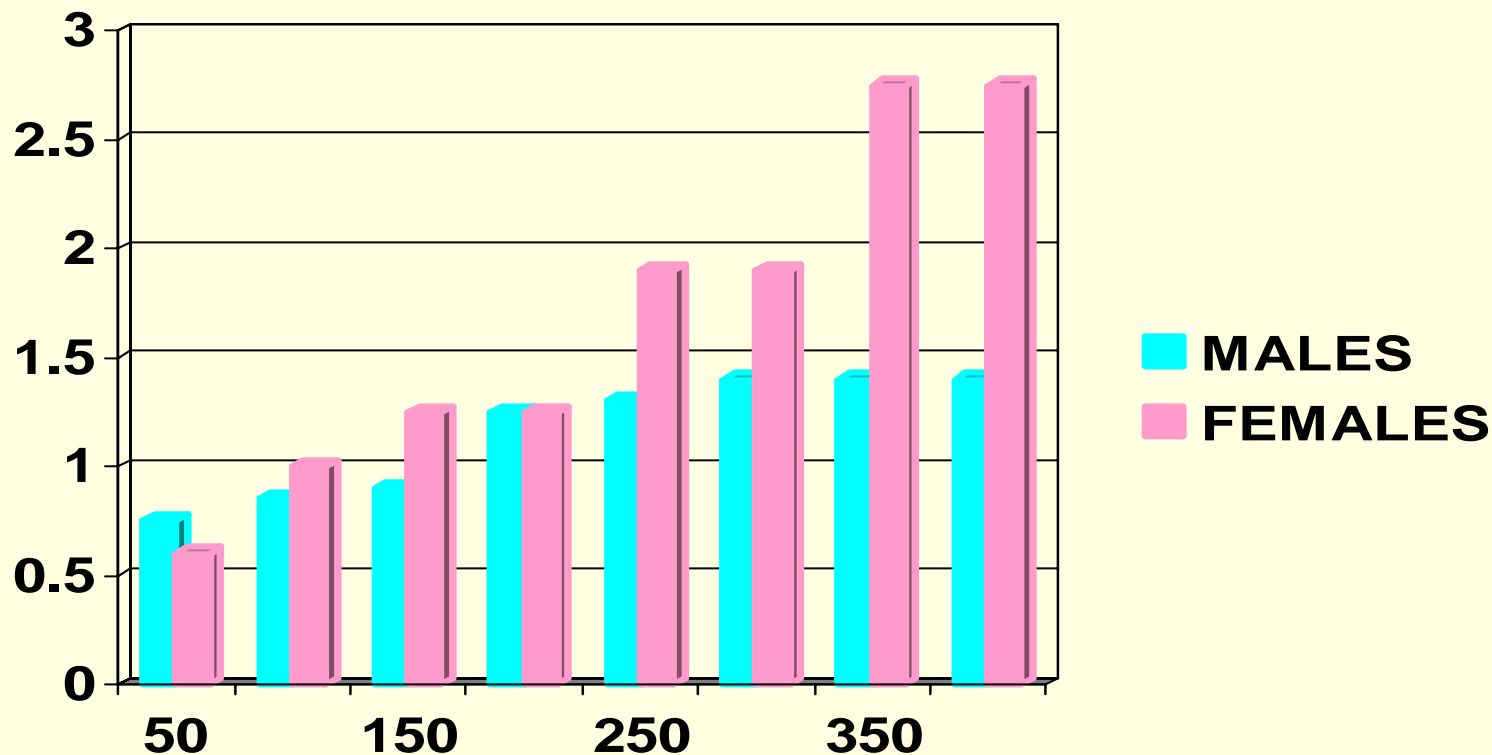
Triglyceride Quartile



Miller, M., Seidler, A., Moalemi, A., et al., "Normal Triglyceride Levels and Coronary Artery Disease Events: The Baltimore Coronary Observational Long-Term Study," *Journal of the American College of Cardiology*, 31(6), 1998, pages 1252-1257.

The Relationship Between Triglycerides (TG) and Relative Risk of Coronary Heart Disease (CHD) in Males and Females

CHD
Relative
Risk



Miller, M., "Is Hypertriglyceridaemia an Independent Risk Factor for Coronary Heart Disease? The Epidemiological Evidence," *European Heart Journal*, 19(Supplement H), 1998, pages H18-H22.

Switch the Entire Metabolism From Glucose-Burning to Fat-Burning

- This lipolytic pathway is the body's second of two primary pathways for energy.
- The human body readily produces all the enzymes involved in fat-mobilization (lipolysis).
- When fat is being mobilized, it neither accumulates nor deposits; instead, it is used as energy.
- Greater quantities of non-carbohydrate food may be consumed as they do not inhibit fat mobilization.

Controlled Carbohydrate Rationale: Alternate Metabolic Pathway

- Stored fat serves as the back-up fuel system.
- The human body cannot store more than a two-day supply of carbohydrate (glycogen).
- When carbohydrate is not available, fat becomes the primary energy fuel.
- Triglyceride is fat.
- When fat is the primary fuel, triglycerides (both stored and in blood) are lowered.
- When fat is the primary fuel, individuals experience increased energy and decreased appetite.

The Controlled Carbohydrate Approach: Therapeutic Principles

- Every person has a level of carbohydrate intake below which weight loss is automatic and a level below which weight maintenance is automatic.
- Find the Critical Carbohydrate Level for Losing (CCLL) and stay at or below this level until goal weight is achieved.
- Once at goal weight, stay at or below the Critical Carbohydrate Level for Maintenance (CCLM).
- From the beginning, select the most nutrient-dense carbohydrates, fats and proteins within the established levels.

How to Achieve Long-Term Success in Weight Control

- Choose a nutritional approach suitable to serve as part of a long-term lifestyle change.
- Choose a nutritional approach that is physically satisfying and suppresses hunger.
- Select a regimen that creates better health and enhanced well-being.
- Attain and maintain goal weight by eating foods that are so enjoyable, there is no desire to change.

The Controlled Carbohydrate Advantage for Long-Term Weight Control

- Provides a metabolic advantage:
 - More fat is burned than on other weight loss programs (calorie for calorie).
- Acts as an appetite suppressant.
- Suitable for long-term adherence:
 - Increased satiety
 - No calorie counting
 - Low-fat food choices not necessary
 - Abundant in basic nutrients

The Controlled Carbohydrate Advantage for Long-Term Weight Control

- Physical improvements noted:
 - Improved lean body mass to fat mass ratio
 - Increased exercise capacity
 - Weight loss maintenance without negative side-effects
- Prevents/corrects hyperinsulin-related conditions:
 - Diabetes
 - Hypertension
 - Cardiac risk factors (high triglycerides, low HDL)

The Controlled Carbohydrate Advantage for Long-Term Weight Control

- Other benefits observed in clinical setting:
 - Less need for sleep
 - Improvement in gastro-intestinal symptoms (irritable bowel syndrome, gastro-esophageal reflux disease, bloating, flatulence)
 - Diminished/eliminated cravings for sweets
 - Improvement in mood
 - Increase in energy

Restricting Carbohydrates Curbs Hunger

- A decrease in hunger was noted after day two of a fast and was attributed to high levels of ketones. “In every case, there was a relationship between hyperketonemia and the loss of appetite.”¹
- The same degree of ketosis was achieved with protein and fat containing foods and elimination of carbohydrate.²
- Therefore, carbohydrate restriction will suppress appetite.

¹ Duncan, G.G., Jenson, W.K., Cristofori, F.C., et al., "Intermittent Fasts in the Correction and Control of Intractable Obesity," *The American Journal of the Medical Sciences*, 1963, pages 515-520.

² Azar, G.J., Bloom, W.L., "Similarities of Carbohydrate Deficiency and Fasting," *Archives of Internal Medicine*, 112, 1963, pages 338-343.

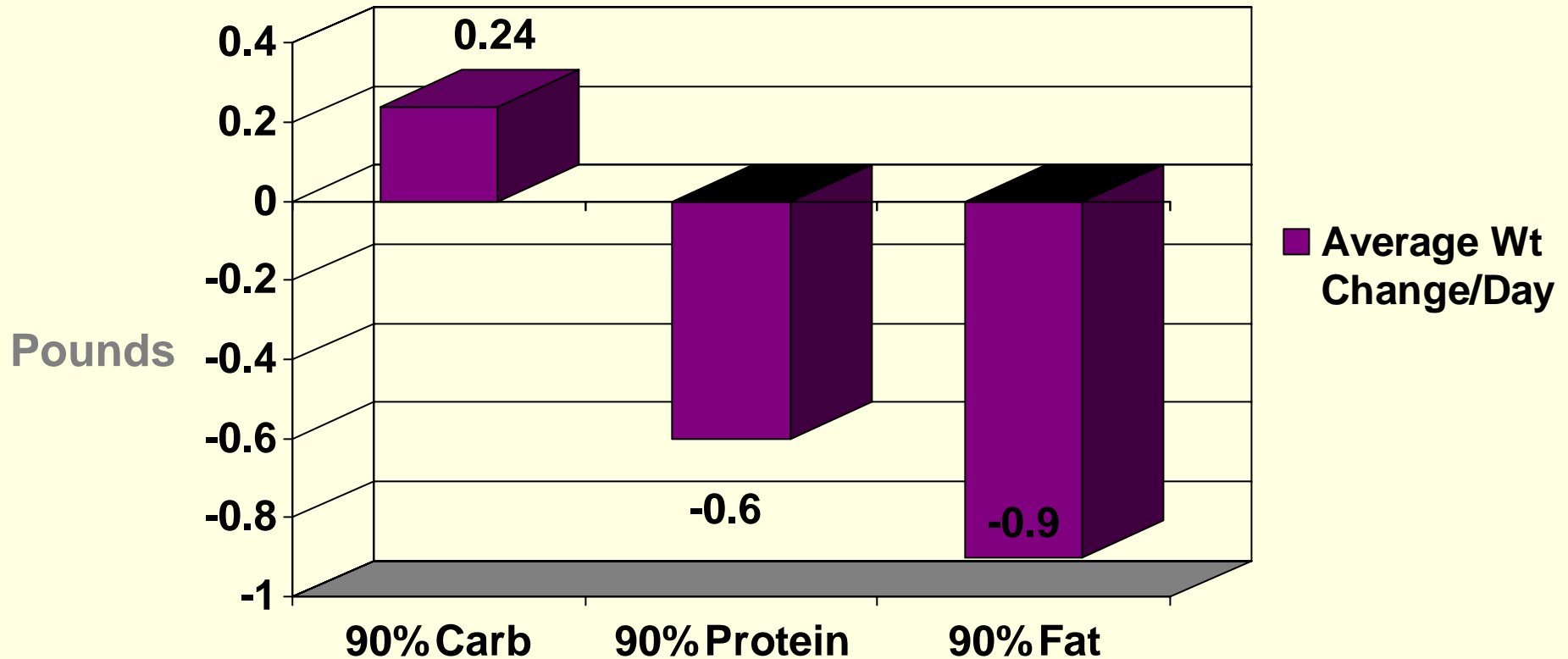
Metabolic Advantage of the Controlled Carbohydrate Approach

- Metabolic advantage refers to the ability of a weight-loss regimen to burn more fat than other diets of different compositions with the same number of calories.
- When a metabolic advantage is demonstrated, it serves to refute the calorie theory.

The Evidence for Metabolic Advantage of Controlled Carbohydrate Approach

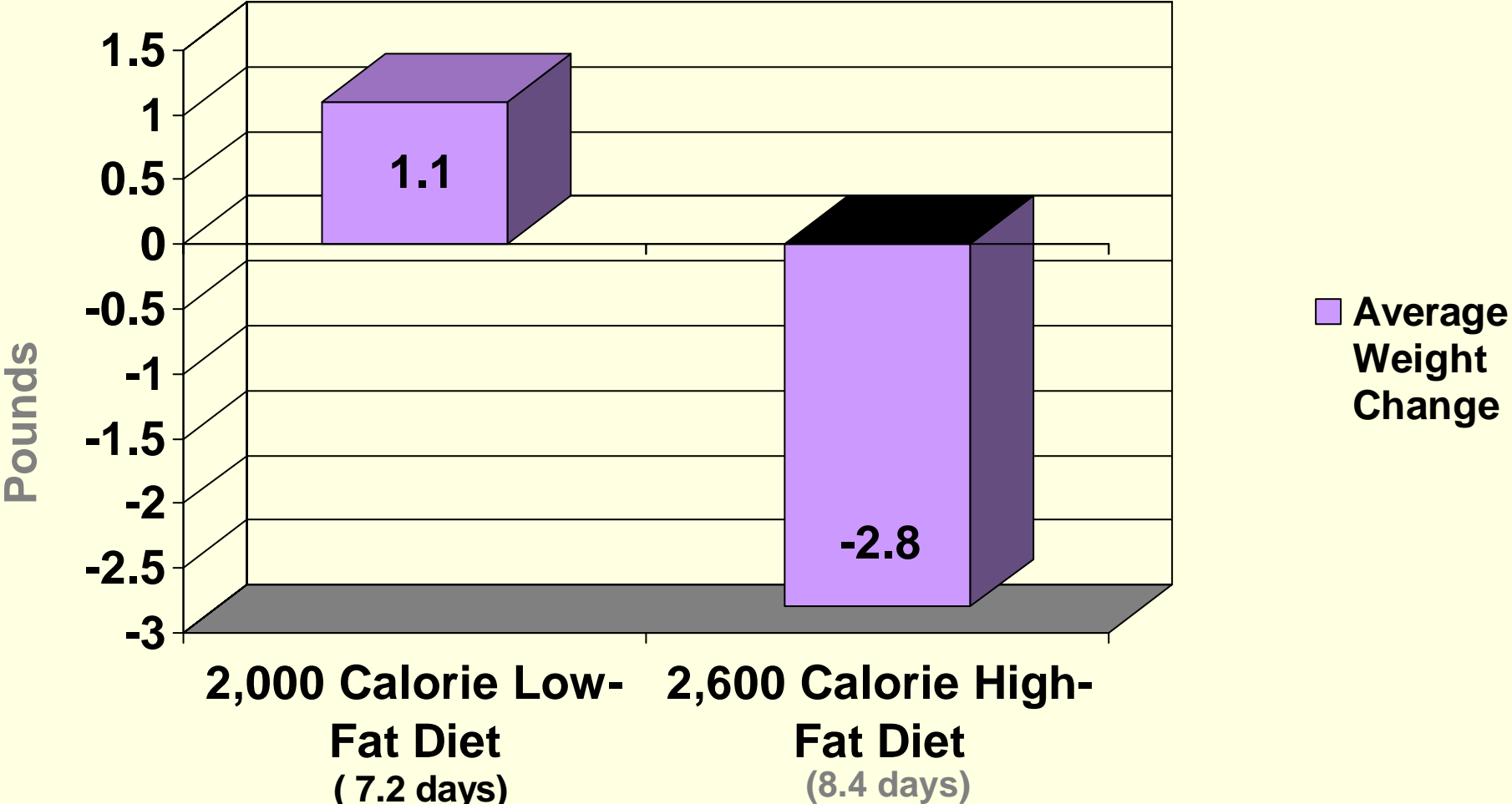
- A 1956 study by Kekwick and Pawan showed a metabolic advantage of 2,350 calories per day.
- A 1965 body composition study by Benoit, et al. demonstrated that a 1,000-calorie diet produced nearly double the loss of body fat as did a total fast.
- A 1971 study at Cornell by Young et al. showed a progressive increase in body fat loss as carbohydrate content dropped from 104 grams to 30 grams.
- A 2000 study by Sondike et al. showed that obese adolescents consuming 66% more calories from a high-fat diet lost twice the weight as did adolescents consuming less calories on a low-fat diet.

Daily Weight Changes on 1,000-Calorie Diets of Different Composition



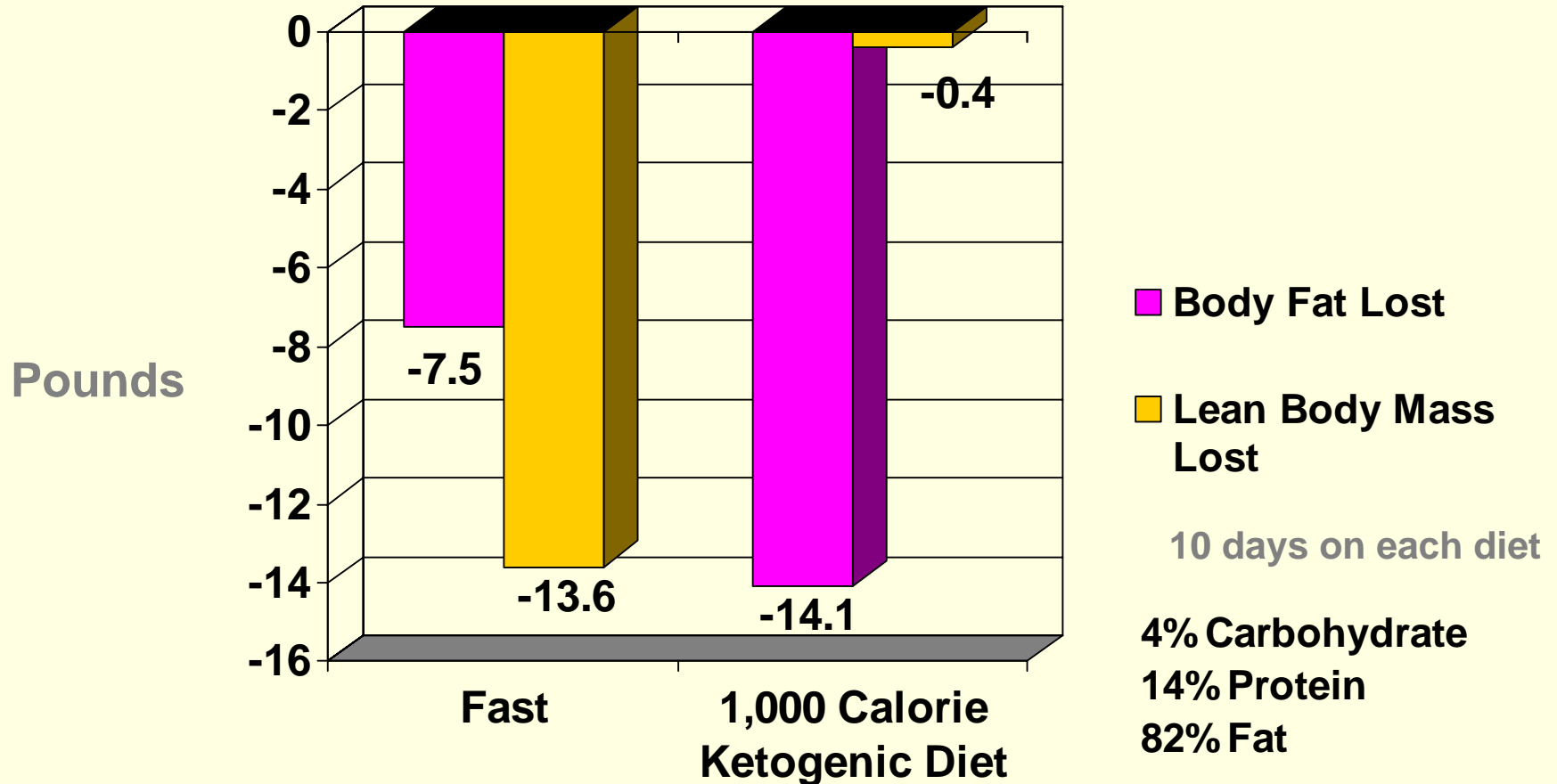
Kekwick, A., Pawan, G.L.S., "Calorie Intake in Relation to Body-Weight Changes in the Obese," *The Lancet*, July 28, 1956, pages 155-161.

Weight Changes on Low-Fat 2,000-Calorie vs. High-Fat 2,600-Calorie Eating Regimens



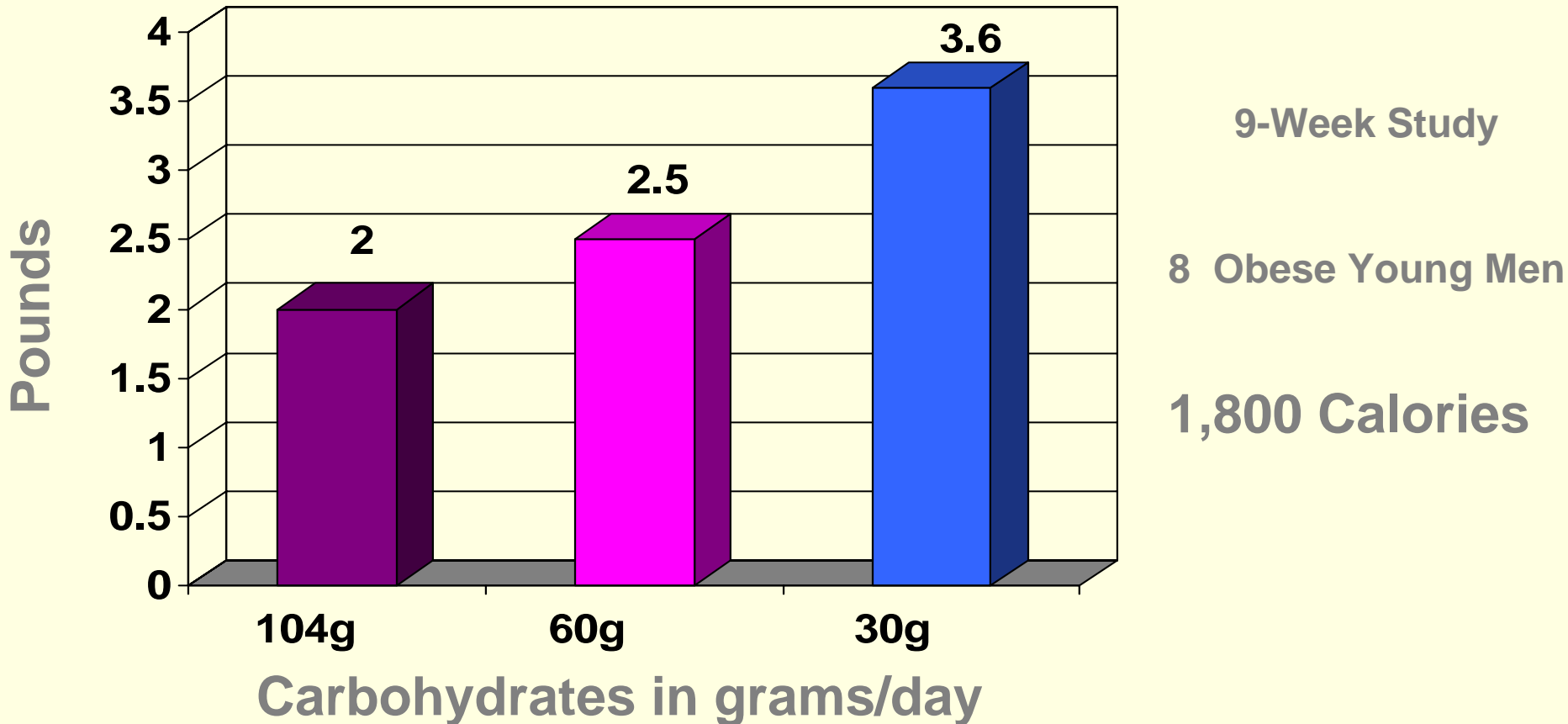
Kekwick, A., Pawan, G.L.S., "Calorie Intake in Relation to Body-Weight Changes in the Obese," *The Lancet*, July 28, 1956, pages 155-161.

Weight Loss Composition on a Ketogenic Diet vs. a Fast



Benoit, F.L., Martin, R.L., Watten, R.H., "Changes in Body Composition During Weight Reduction in Obesity: Balance Studies Comparing Effects of Fasting and a Ketogenic Diet," *Annals of Internal Medicine*, 63(4), 1965, pages 604-612.

Pounds of Body Fat Lost Per Week on Varying Grams of Carbohydrate Intake



Young, C.M., Scanlan, S.S., Im, H.S., et al., "Effect on Body Composition and Other Parameters in Obese Young Men of Carbohydrate Level of Reduction Diet," *The American Journal of Clinical Nutrition*, 24, 1971, pages 290-296.

Weight Change Using High-Carbohydrate and High-Fat Diets

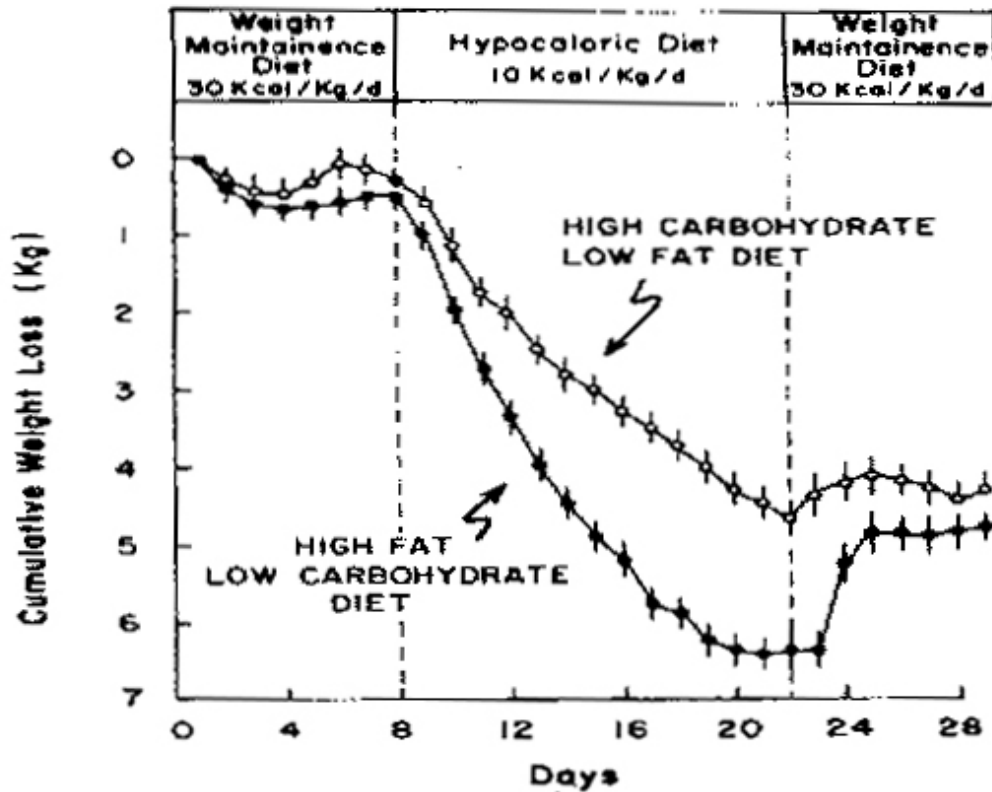


FIG. 1. Weight loss during weight maintenance dietary period, hypocaloric diet period, and reinstatement of weight maintenance dietary period. Mean \pm SEM ($n = 10$).

14-day randomized reduction diet

High-Fat Diet:
70% fat,
10% Carbohydrate

High-Carbohydrate Diet:
10% fat,
70% Carbohydrate

Both: 1/3 usual caloric intake

A 4-Week Randomized Dietary Intervention Trial

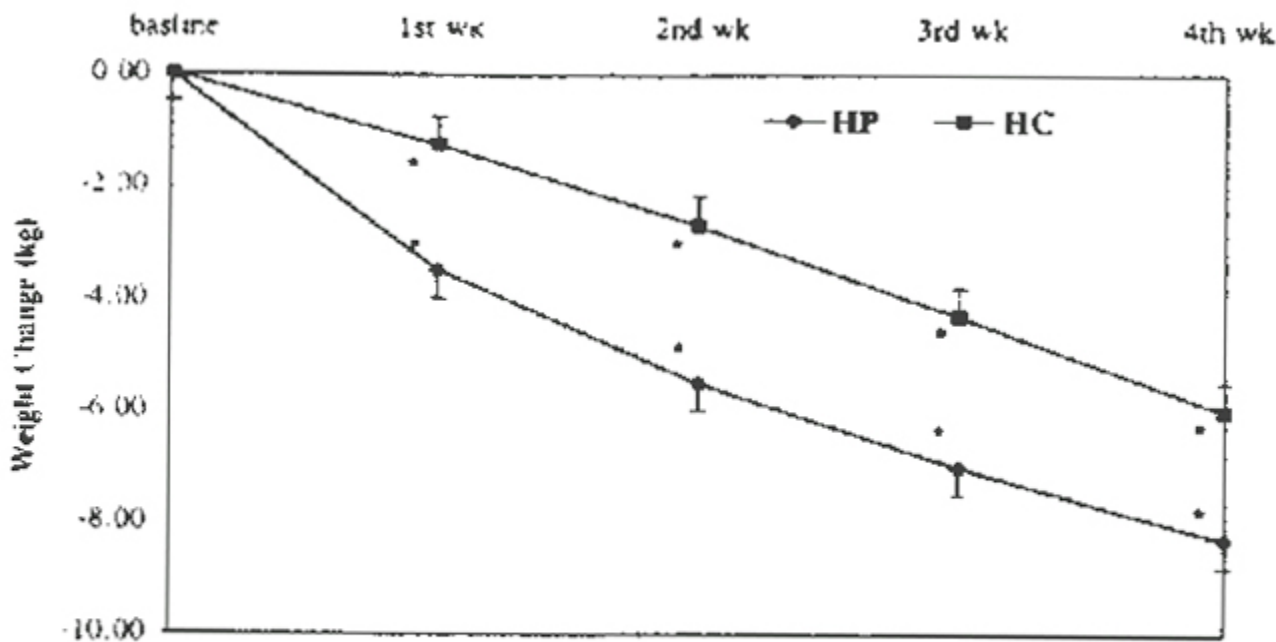


Figure 1 Effect of hypoenergetic HP vs HC diet on changes in body weight in hyperinsulinemic obese male subjects. *Significant difference between the two groups at $P < 0.05$.

13 Obese normoglycemic, hyperinsulinemic males

High-Protein Diet (n=7):
45% Protein
25% Carbohydrate

High-Carbohydrate Diet (n=6):
12% Protein
58% Carbohydrate

Baba, N.H., Sawaya, S., Torbay, N., et al., "High Protein vs High Carbohydrate Hypoenergetic Diet for the Treatment of Obese Hyperinsulinemic Subjects," *International Journal of Obesity*, 11, 1999, pages 1202-1206.

The Role of Ketones

- Fat delivers energy via ketones just as carbohydrate delivers energy via glucose.
- Enzymes are present within all cells, including the brain, to convert ketones into fuel.

Ketones as a Fuel Source

- Results in decrease in appetite.
- Insulin is not involved in ketone production.
- Lowered insulin requirements decrease:
 - Triglycerides
 - Blood Pressure
 - Adrenaline, cortisol
 - PCOS, breast cancer death rate

Ketone Body Metabolism

- Low-carbohydrate diets result in increased ketone production in liver (ketogenesis).
- Nearly every cell in the body can use ketones as an alternative energy source (ketolysis).
- “Physiological” versus “diabetic” hyperketoacidosis:

Fed State:	0.1 mmol/L
Overnight Fast:	0.3 mmol/L
Ketogenic Diet:	1-3 mmol/L
>20 Days Fasting:	10 mmol/L
Uncontrolled Diabetes:	>25 mmol/L
- Urinary ketone excretion is in direct proportion to plasma concentrations.

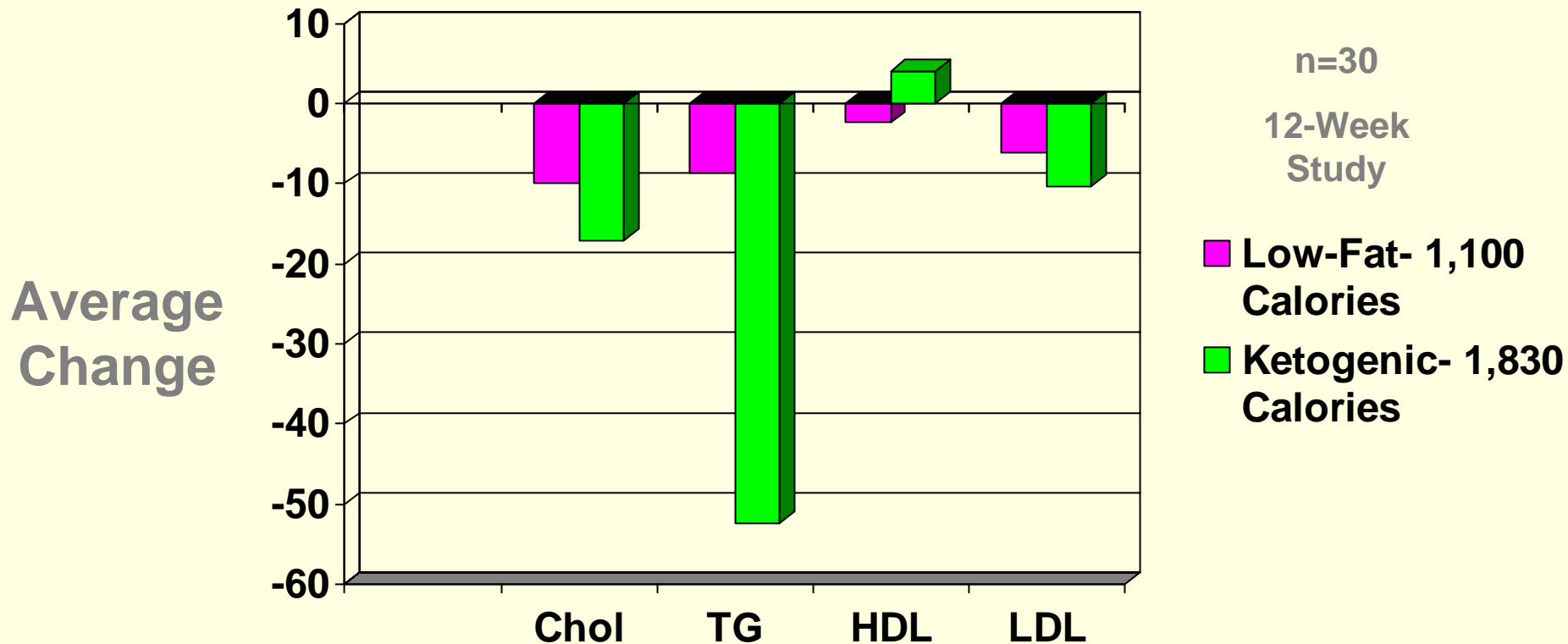
The Human Metabolic Response to Chronic Ketosis Without Caloric Restriction: Physical and Biochemical Adaptation

Summary:

“In view of the tests done to screen for ill effects of the EKD, the remarkably benign nature of a diet providing 85% of calories as fat is notable. After 4 weeks there was no measurable impairment of hepatic, renal, cardiac, or hematopoietic function. The serum uric acid level, elevated by competition from ketone bodies for excretion, was almost back to normal by that time.”

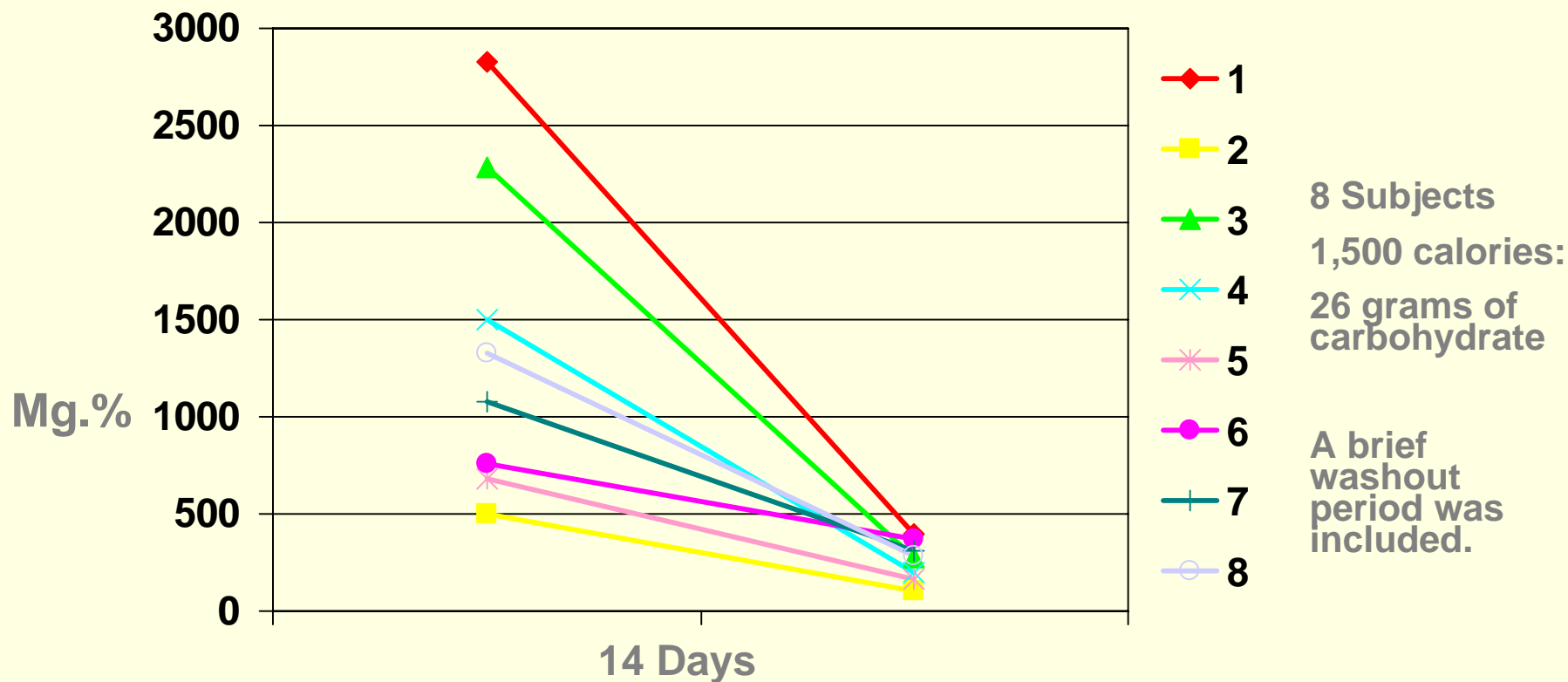
Phinney, S.D., Bistrian, B.R., Wolfe, R.R., et al., "The Human Metabolic Response to Chronic Ketosis Without Caloric Restriction: Physical and Biochemical Adaptation," *Metabolism*, 32(8), 1983, pages 757-768.

Comparison of Conventional Low-Fat Diet With a Non-Energy Restricting, Controlled Carbohydrate, Ketogenic Program in Obese Adolescents



Sondike, S.B., Copperman, N.M., Jacobson, M.S., "Low Carbohydrate Dieting Increases Weight Loss but not Cardiovascular Risk in Obese Adolescents: A Randomized Controlled Trial," *Journal of Adolescent Health*, 26, 2000, page 91.

Triglyceride Changes on a Controlled Carbohydrate, High-Fat Regimen



Reissell, P.K., Mandella, P.A., Poon-King, T.M.W., et al., "Treatment of Hypertriglyceridemia," *The American Journal of Clinical Nutrition*, 19, 1966, pages 84-98.

20- to 25-Gram Carbohydrate Nutritional Approach: Effect on Serum Lipids

<u>Variables (mg/dl)</u>	<u>Baseline mean (SD)</u>	<u>Week 16 mean (SD)</u>	<u>% Change</u>
Cholesterol	212.0 (34.4)	201.4 (40.5)	- 5.6
LDL	132.9 (28.8)	129.8 (37.5)	NS
HDL	53.4 (13.6)	55.9 (12.4)	+ 8.8
Chol/HDL	4.2 (1.3)	3.7 (1.6)	- 16.7
Triglycerides	122.3 (59.6)	78.6 (35.1)	- 42.6

n=40 overweight males and females 6-month prospective clinical trial

* *p* < 0.05, comparing change from baseline to week 16

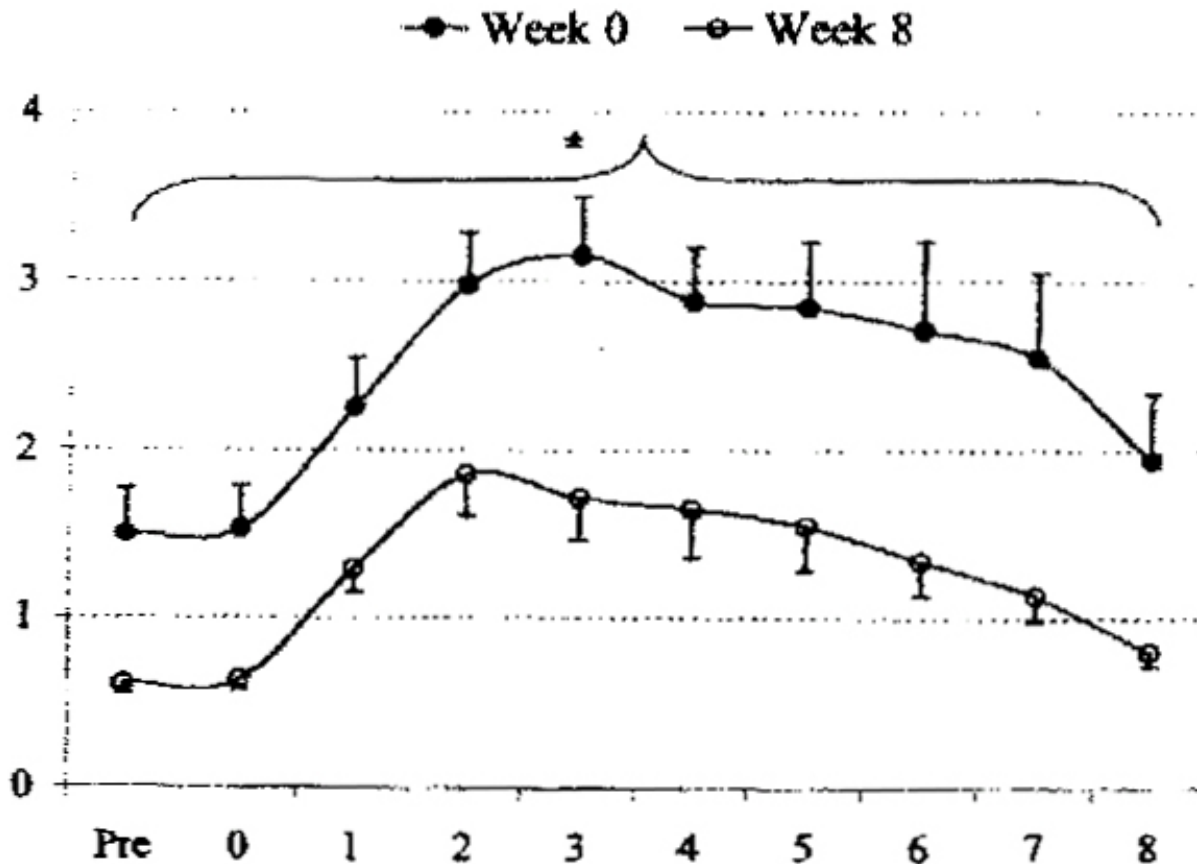
Yancy, W. S., Bakst, R., Bryson, W., et al., "Effects of a Very-Low-Carbohydrate Diet Program Compared With a Low-Fat, Low-Cholesterol, Reduced Calorie Diet," October 7, 2001, *North American Association for the Study of Obesity Annual Meeting*, Quebec City, Canada.

High-Fat Controlled Carbohydrate Approach Improves Lipid Profile

	Baseline	12 Mo.	% change
Weight (lbs)	225	184	-18
Total Chol (mg/dl)	285	204	-28
TG (mg/dl)	280	190	-32
HDL (mg/dl)	40	52	+30
LDL (mg/dl)	176	115	-35
VLDL (mg/dl)	49	39	-20

Reed, T., Shakir, K.M.M., Harari, A.E., et al., "High-Fat, Low-Carbohydrate Diet Improves Symptoms of Postprandial Hypoglycemia," 2000, *Abstract of the 81st Annual Meeting of the Endocrine Society*.

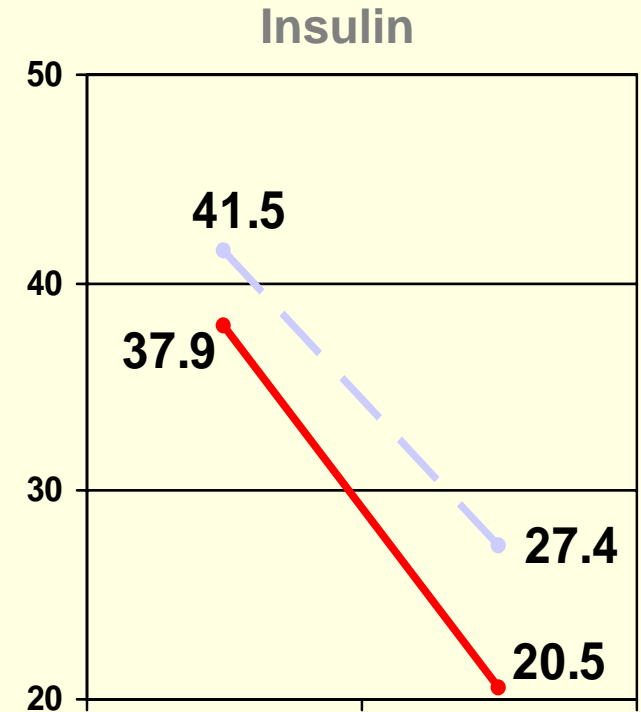
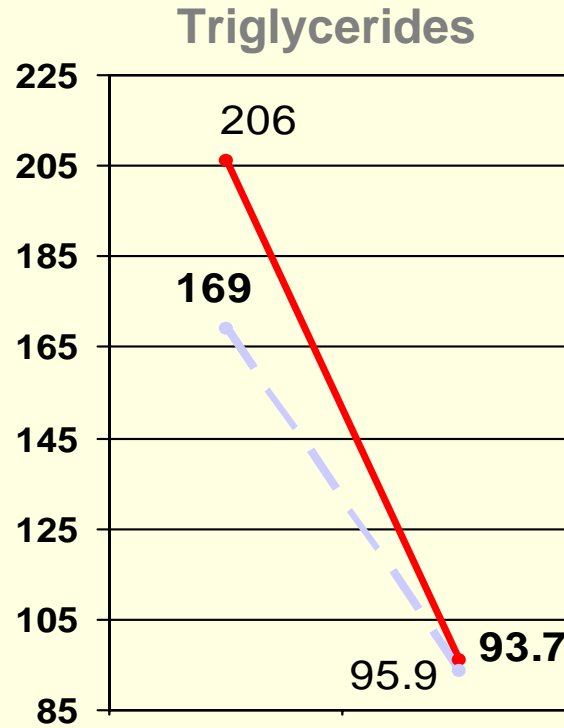
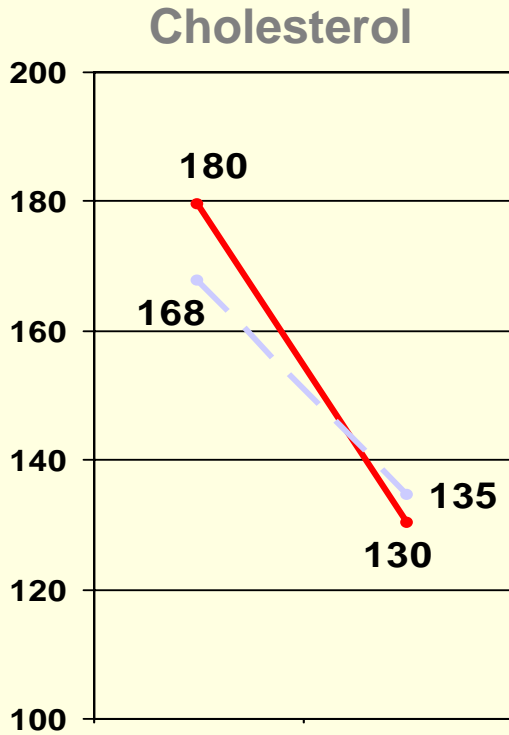
Effect of a Ketogenic Diet on Postprandial Triglycerides in Normal Men



65% Fat,
10% Carbohydrate

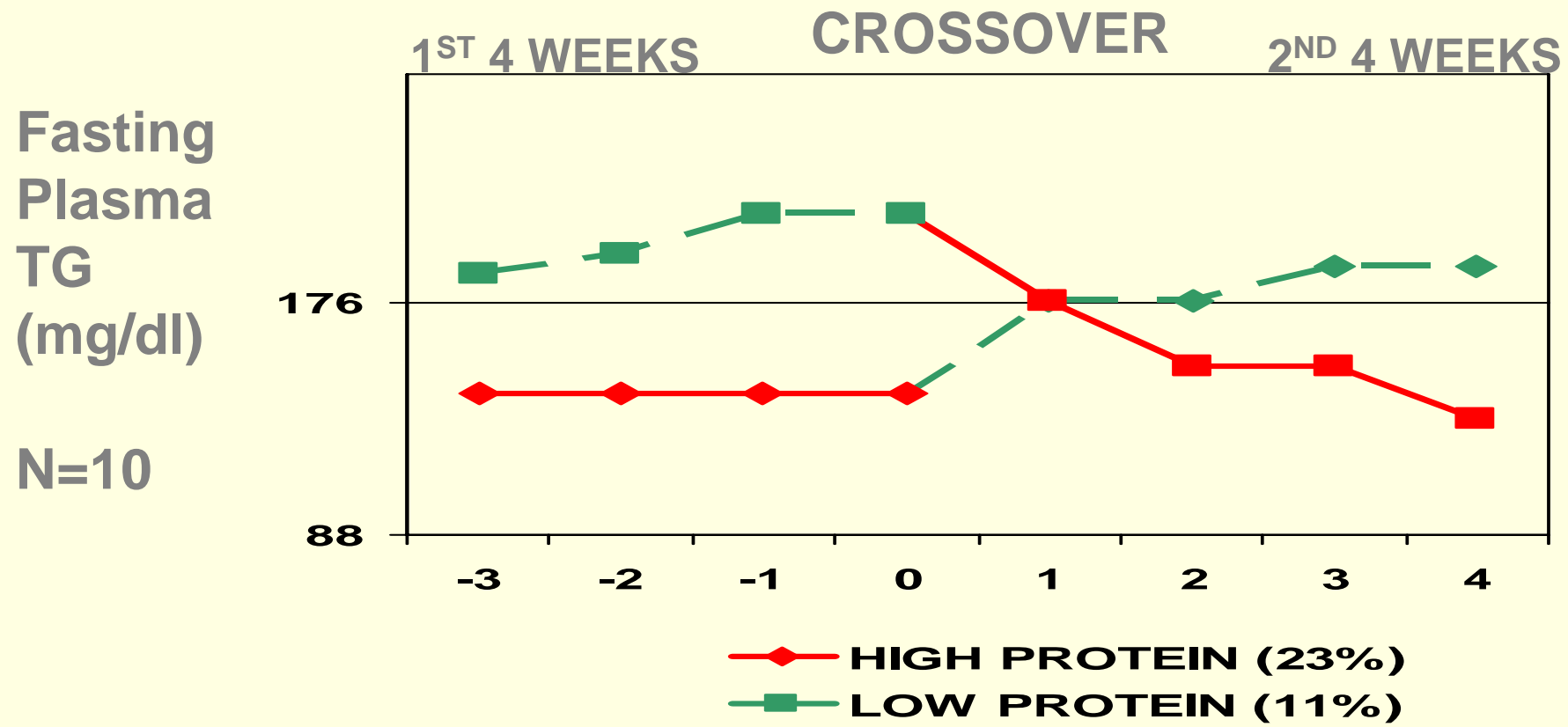
Volek, J.S., Gómez, A.L., Kraemer, W.J., "Fasting Lipoprotein and Postprandial Triacylglycerol Responses to a Low-Carbohydrate Diet Supplemented With N-3 Fatty Acids," *Journal of the American College of Nutrition*, 19(3), 2000, pages 383-391.

Substituting Protein For Carbohydrate: 4-Week Randomized Dietary Intervention Trial



—●— 45% Protein, Carbohydrate 25% n=6
- -●- - 12% Protein, Carbohydrate 58% n=7

High- and Low-Protein Diet, Crossover Study: Effect on LDL-C and TG (8 weeks)



Wolfe, B.M., Giovannetti, P.M., "Short-Term Effects of Substituting Protein for Carbohydrate in the Diets of Moderately Hypercholesterolemic Human Subjects," *Metabolism*, 40(4), 1991, pages 338-343.

Relationships Between Fibrinogen and Insulin Resistance

- There was a significant positive correlation between fibrinogen and insulin resistance ($r=0.76$, $p<.0001$).
- “Only insulin sensitivity appeared to account for the ability to predict fibrinogen values.”

Raynaud, E., Perez-Martin, A., Brun, J., et al., "Relationships Between Fibrinogen and Insulin Resistance," *Atherosclerosis*, 150(2), 2000, pages 365-370.

Daily Menu With 20 Grams of Carbohydrate

Breakfast

Three Egg Omelet With Avocado,
Mozzarella Cheese and Tomato
Organic Nitrate-Free Bacon (2 Strips)
Decaffeinated Coffee With Cream

Lunch

Beef Round (8 oz)
Spinach and Mixed Leaf Salad With Mushrooms,
Onions, Celery and Parmesan Cheese
Club Soda

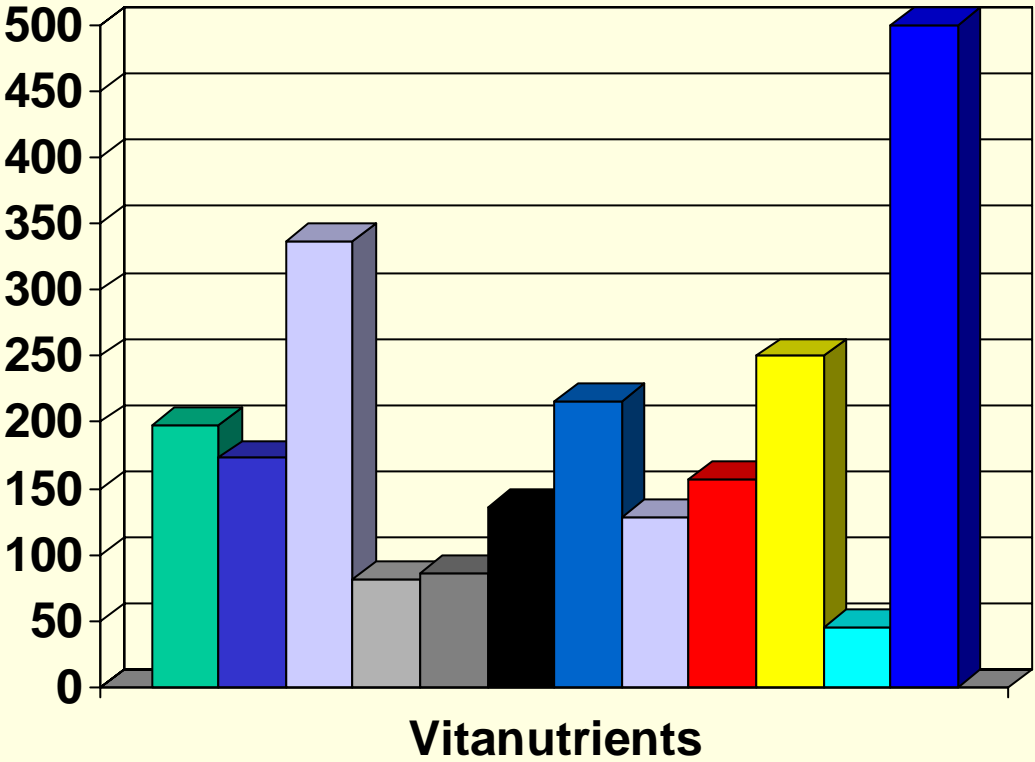
Dinner

Broiled Salmon (9 oz)
Kale Topped With Garlic, Lemon and Sesame Seeds
Spring Water

Nutrient Analysis of Sample Menu With 20 Grams of Carbohydrate Based on Daily Values/RDI

2,000-Calorie Diet

Percent of Daily Values

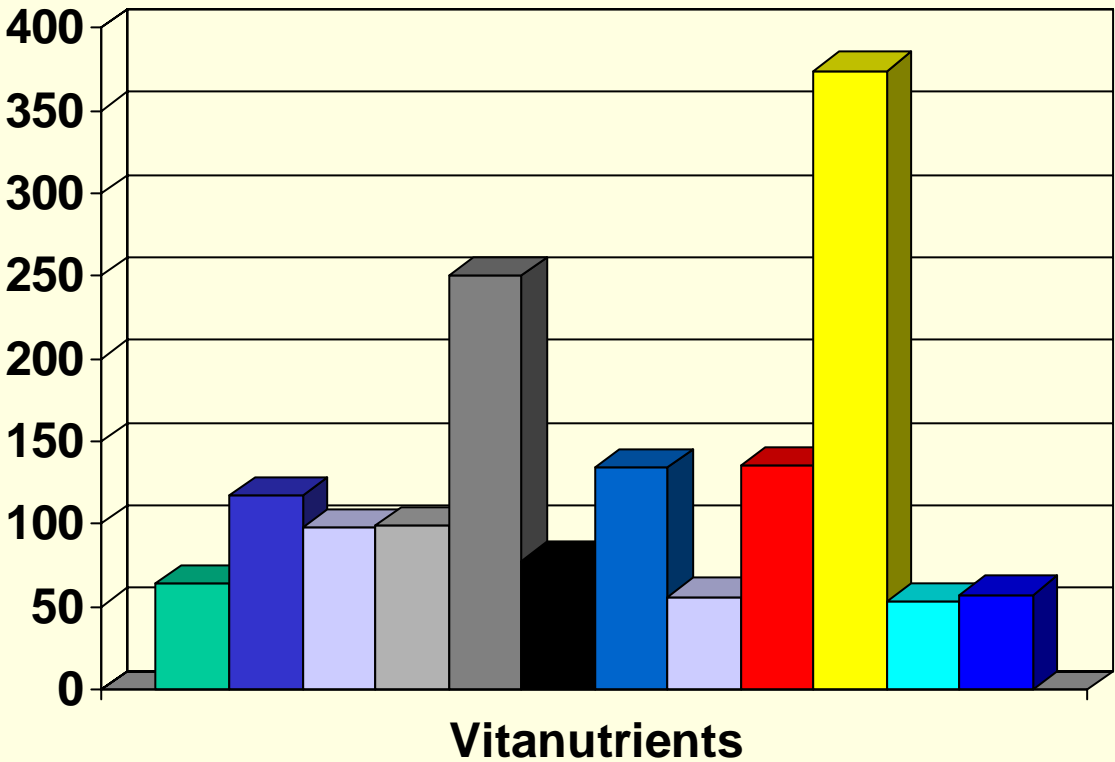


- Vitamin A
- Vitamin C
- Vitamin D
- Vitamin E
- Thiamin
- Riboflavin
- Niacin
- Pyridoxine
- Folate
- Cobalamin
- Pantothenic Acid
- Vitamin K

Nutrient Analysis of Sample Menu With 20 Grams of Carbohydrate Based on Daily Values/RDI

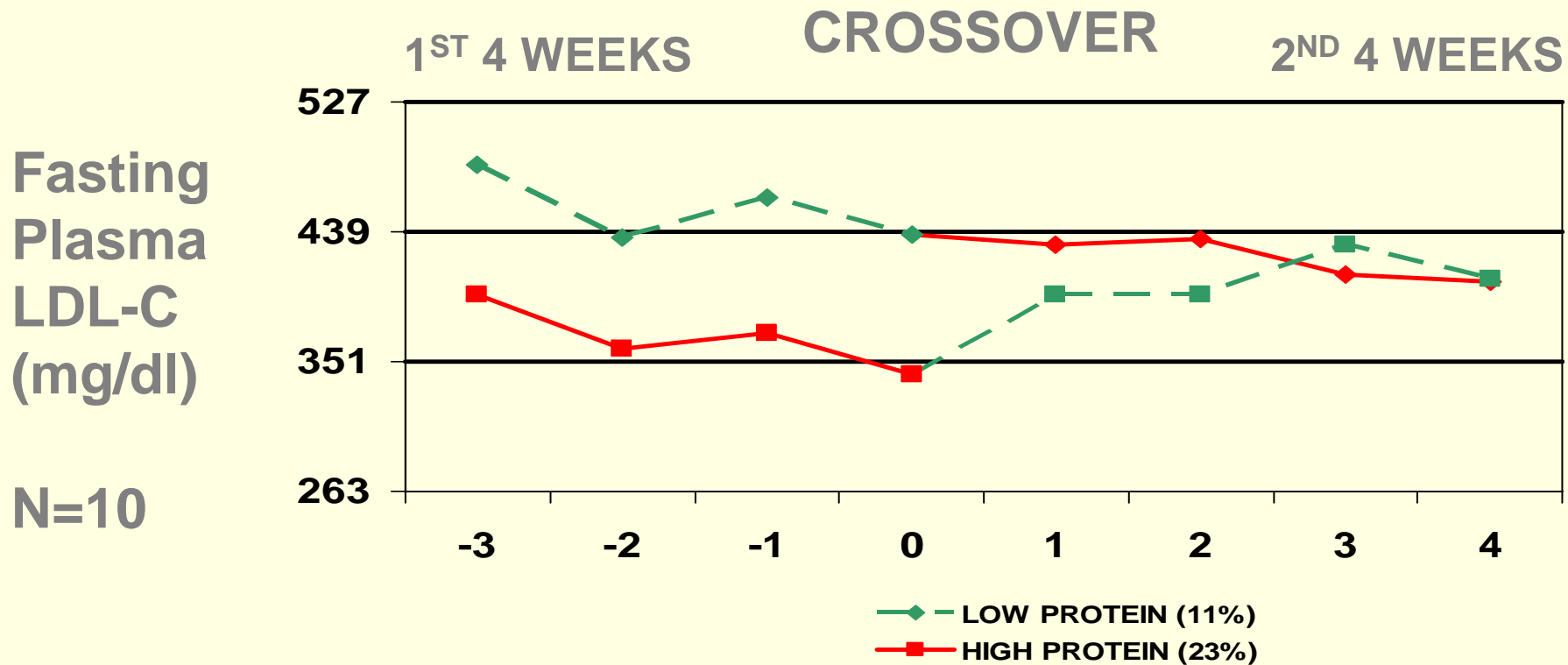
2,000-Calorie Diet

Percent of Daily Values



- Sodium
- Potassium
- Calcium
- Iron
- Phosphorus
- Magnesium
- Zinc
- Copper
- Manganese
- Selenium
- Chromium
- Molybdenum

High- and Low-Protein Diet, Crossover Study: Effect on LDL-C and TG (8 weeks)



Wolfe, B.M., Giovannetti, P.M., "Short-Term Effects of Substituting Protein for Carbohydrate in the Diets of Moderately Hypercholesterolemic Human Subjects," *Metabolism*, 40(4), 1991, pages 338-343.