FROM ATKINS TO THE ZONE

THE SCIENCE BEHIND THE SPIN

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MEDICAL GRAND ROUNDS

JANUARY 13, 2000

This is to acknowledge that Shalini Reddy, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program

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Her interests include medical education and the effects of high protein diets on mineral metabolism.

I. INTRODUCTION

CASE: M.K. is a 54 year old white female who presents for a routine visit. She has no acute medical complaints but reports a gradual weight gain over the past three years. She is a flight attendant and says that she has poor self esteem at work because of the weight gain. She currently weighs 210 pounds and is 5'8". She would like to lose 70 pounds over the next 3 months and has started the Atkins' diet. She has tried numerous other "crash" diets in the past that have resulted in rapid weight loss followed by weight regain as soon as she resumes a normal diet. She wants to know if you think the Atkins' diet would be safe and effective for her.

The objective of today's Grand Rounds is to provide information that will help you answer her question. The outline of today's talk is as follows:

1) Background information on obesity and standard treatment modalities.

2) Introduction to popular weight reducing diets.

3) The principles of two popular weight-reducing diets (low carbohydrate diets)

4) Review of the scientific literature

5) Advice for your patient

II. BACKGROUND

A. OBESITY

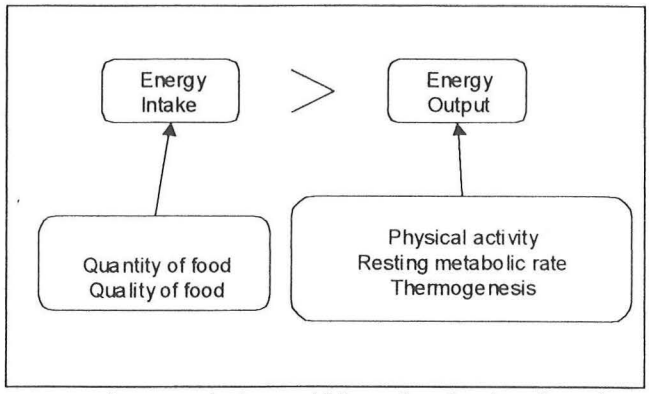
The National Heart, Lung, and Blood Institute of the NIH recently published revised guidelines for the identification, evaluation and management of overweight and obesity in adults. They used evidence-based techniques to define body mass index based criteria for overweight and obesity. BMI is calculated as weight (kg)/height $(m)^2$ or weight (lb)/height $(in)^2$ x 703. (1) A BMI $\geq$ 25 is overweight and a BMI $\geq$ 30 is obese. (2) A BMI $\geq$ 25 correlates with increased mortality. (3) Waist circumference correlates well with coronary artery disease risk and is increased if the circumference is greater than 102 cm (40 in) in men and over 89 cm (35 in) in women. (2)

Over the past two decades, there has been a marked increase in the prevalence of obesity in the United States. The 1988 -1994 National Health and Nutrition Examination Survey (NHANES III) estimated that among men and women between the ages of 20 - 74, 32% are overweight (BMI 25-29) and 22.5% are obese. (4) 63% of men are obese or overweight and 55% of women are obese or overweight. (5) Complications of obesity account for 4.32% - 6.3% of health care costs and will likely account for greater amounts as the diseases that complicate obesity become clinically apparent. (6) (7) Obesity has become a problem of epidemic proportion in industrialized countries. It is estimated that 280,000 annual deaths in US adults can be attributed to obesity. (8)

The rapid increase of the obesity epidemic is perplexing. While the etiology of this epidemic is largely unknown, the cause of obesity can be viewed simplistically as a problem with physics.

The human body follows the basic laws of thermodynamics: net weight gain or loss is determined by the balance between energy intake and energy output. (Figure 1)

Figure 1 : Etiology of Obesity



The components of energy intake and output are reviewed in detail in Dr. Margo Denke's Grand Rounds from 4/3/1997 and will be briefly reviewed here. (9) Energy intake is largely determined by the quantity of food consumed. The quantity of food consumed is governed by appetite. Appetite, in turn, is regulated by emotional, behavioral, neurohormonal, environmental and genetic factors. Great strides are being made in understanding appetite regulation. Although obesity has been commonly viewed as a disease of poor self-control, the discovery of leptin 6 years ago has altered our thinking about appetite regulation. The exact role of leptin in humans is unclear, but it appears to act through a myriad of second messengers in the regulation of appetite. (10) There is a complex interaction between a variety of neurohormones and dietary factors. Neuropeptide Y administration, for example, increases the consumption of carbohydrates in rats, specifically of sucrose-containing foods. (11) Many of the current popular diets point to insulin as the main culprit in obesity. Insulin increases glycogen, protein and fatty acid synthesis and this is seen as proof of its role in the pathogenesis of obesity. Much remains to be learned about the role of insulin in obesity. However, there is currently evidence that obesity and a sedentary lifestyle result in abnormalities in insulin signaling. These abnormalities are reviewed in detail in Dr. Nicola Abate's Grand Rounds January 6th, 2000. (12)

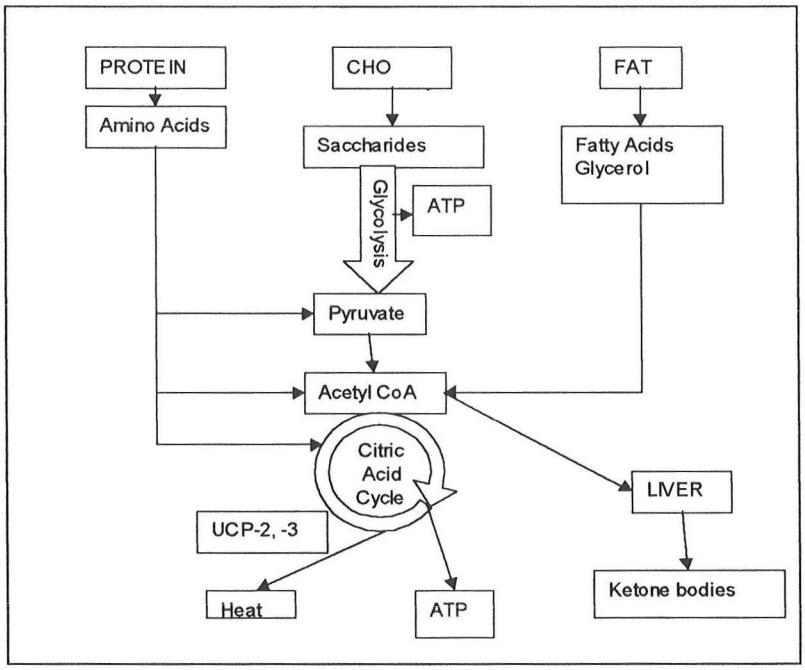
The type of food (quality) is important in regulating satiety and palatability, which in turn influences the quantity of food consumed. Overfeeding studies suggest that protein has a significant short-term satiating effect when compared to carbohydrates or fat. (13) (14) This finding is important to consider when one looks at the caloric content of protein, fat and carbohydrate. Protein and carbohydrates contain four calories per gram, and fat contains nine calories per gram. Over-consumption of fat induces gastric distention and reduces gastric emptying thus inducing a feeling of fullness. However, the addition of fat to a meal increases palatability and may lead to excess consumption of energy dense meals. (15) In addition, fat is oxidized less readily than carbohydrates or protein and is instead preferentially stored as adipose tissue (16).

Shah and Garg (17) reviewed the available literature on the relationship between macronutrient composition and obesity. Short and long term nutrient utilization and energy expenditure studies, epidemiologic data as well as intervention studies were included. Short term nutrient utilization studies comparing isoenergeic high fat versus high carbohydrate diets demonstrate that replacing the fat content of a meal with carbohydrates results in a negative fat balance. Short-term overfeeding studies demonstrate that overfeeding with fat results in fat storage while overfeeding with carbohydrates results in limited de novo lipogenesis. Long term studies, however, demonstrate that overfeeding with fat or carbohydrates results in increased fat stores.

The way our bodies process macronutrients has not changed substantially over the past 20 years, so why have we gotten so obese? It appears that our ancient genes are incompatible with our modern environment and that we have evolved to have a predilection for obesity. The thrifty gene theory proposes that the genetic makeup of certain populations predisposes to fat storage and insulin resistance. This confers a survival advantage to these populations during times of famine. (18) Our genes have sabotaged us during these times of "continuous feast." Americans are eating more calories and are leading more sedentary lives. Between 1977 and 1996, the number of calories consumed increased by 200 kcal per day for men and 100 kcal per day for women (19). Americans dine out more than nine times each week with a tendency to consume energy dense, high fat meals. The availability, palatability and over-consumption of nutritionally empty but calorically rich snack foods has also probably contributed to weight gain. (20)

The components of energy output are resting metabolic rate, thermogenesis and physical activity. Of these, the resting metabolic rate or the "cost of sustaining life" accounts for about 60-70% of total energy expenditure and is largely governed by non-modifiable factors. Age, body weight and height are all included in determinations of the resting metabolic rate. Genetics appears to play a large role in determining resting metabolic rate as well.

Figure 2: Macronutrient Catabolic Pathways

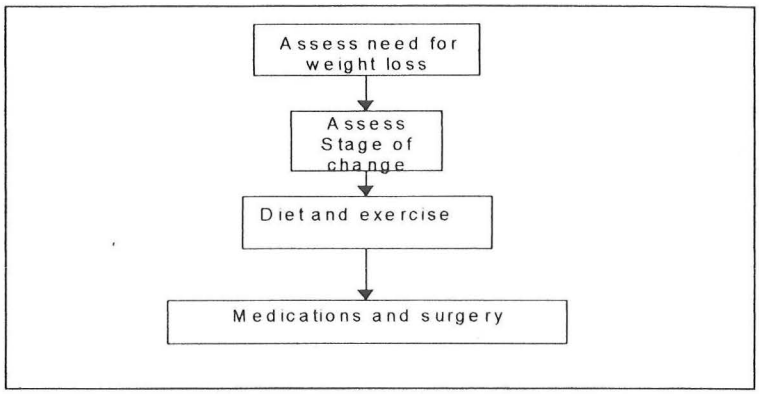


Thermogenesis accounts for approximately 15% of daily energy requirements. Much of this is expended to maintain body temperature. There are some dietary factors that can increase thermogenesis. Caffeine, for example increases thermogenesis for several hours after ingestion. A number of recent interesting developments in the area of uncoupling proteins suggests that fasting may also increase thermogenesis. Uncoupling proteins 2 and 3 are located in the skeletal muscle and adipose tissue of humans. These proteins uncouple respiration from ATP synthesis and thus result in the expenditure of energy as heat. (Figure 2) During times of fast, there is increased expression of UCP-2 and -3 mRNA in lean and obese subjects. (21) Returning to Figure 1, this would result in increased thermogenesis and thus a net increase in energy output.

The final and most readily modifiable component of energy output is physical activity. The 1997 National Health Interview survey found that 40% of U.S. adults were sedentary and engaged in no physical activity. (22) This trend is mirrored in children and adolescents who are watching more television and participating in fewer bouts of strenuous exercise. This combination correlates with increased BMI. (23)

B. STANDARD THERAPY OF OBESITY

Figure 3: Treatment of Obesity.



Obesity is clearly a multifactorial and complex disease influenced by genetics, environment and behavior. The prevailing opinion is that obesity is 50 - 75% genetic and 25 - 50% environmental. While great strides are being made in elucidating the etiologies of obesity, much remains to be learned. Therapeutic modalities have, therefore, been limited by our incomplete understanding of the mechanisms of obesity. Current standard therapy for obesity consists primarily of diet, exercise and medications. (Figure 3)

Table 1 : Risk Factors for CVD in Overweight and Obese Individuals

Increased waist circumference (>35 in women; >40 in men)
Established coronary artery disease
Non cardiac atherosclerotic disease
Type 2 Diabetes
Obstructive sleep apnea
Cardiovascular risk factors: Smoking; Hypertension; family history;high LDL; low HDL; age > 45 for men; age >55 for women or postmenopausal

Obesity therapy should begin with an assessment of whether the patient needs to lose weight. A BMI chart is included in Appendix A to guide this decision. Weight loss therapy is recommended for patients with a BMI $\geq$ 30 or those with a BMI $\geq$ 25 with a high risk for cardiovascular disease (CVD). The latter group merits further clarification. These risks are shown in Table 1. (2)

Once it has been determined that the patient would derive health benefits from weight reduction, his or her willingness to lose weight should be assessed. The Stage of Change Construct provides a model that characterizes an individual's readiness to change based on past behavior and intended behavior. (24) This model has been used extensively in smoking cessation programs and is now being used to counsel patients about exercise and low fat diets. (25) It is also be helpful for matching a weight reducing intervention with the patient's readiness to lose weight. The five stages of change are:

1) Pre-contemplation: not intending to change nor planning to change in the next 6 months.

2) Contemplation: thinking about changing behavior in the next 6 months.

3) Preparation: expressing proximate intention to meet the behavior change goal within the next thirty days.

4) Action: actively making behavioral changes but for less than six months.

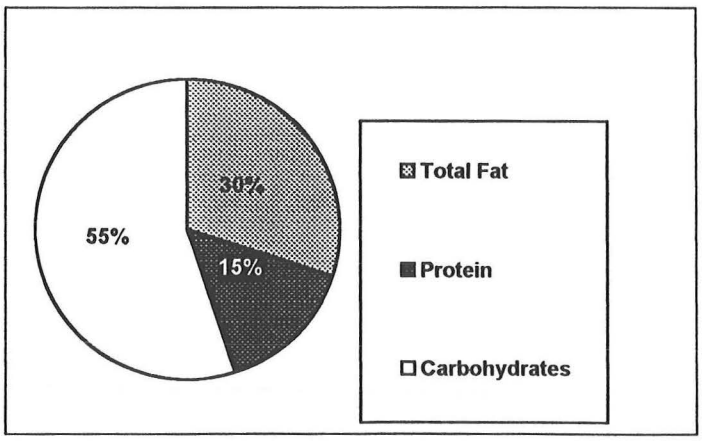
5) Maintenance: sustaining the behavioral change for longer than six months.

A general health survey conducted in the US and Australia found that 45% of all respondents (in the general population) were in the pre-contemplation stage for trying to lose weight. (26) Most of the patients who ask questions about popular weight reduction diets are in the preparation, action or maintenance stages of change. These individuals provide us with a prime opportunity to counsel them about standard weight reduction therapies.

Standard weight reduction diets are typically hypocaloric diets. They may be either moderately low or very low in calories. The caloric content of these diets is calculated using the patient's baseline caloric requirements which incorporates his or her age, sex, weight, height, level of physical activity and injury factor. A moderately low calorie diet provides a deficit of 500 to 1000 calories per day. For a typical overweight woman, this diet contains a daily caloric intake of 1,000 to 1,200 kcal per day. For an average man, this diet is 1,200 - 1,500 kcal per day. Low calorie diets alone result in modest weight reduction (8% of body weight) over 6-12 months. (2) Diets low in fat typically result in reduced caloric intake and thus decreased weight.

A very low calorie diet (VLCD) results in severe energy restriction to a total of $\leq$ 800 kcal per day. This diet is designed to effect a rapid weight reduction. The main role for a very low calorie diet is in preparing a patient for surgery in which a rapid weight loss could significantly improve outcomes. (27) VLCD's can cause gallstones, nutritional deficiencies and electrolyte imbalances and require strict medical supervision. These diets do not appear to be superior to moderately low calorie diets for the maintenance of weight loss. (28)

Figure 4: Composition of Recommended Weight Loss Diet



The standard weight reduction diet recommended by dieticians focuses on patient food preference and meeting recommended daily allowances of nutrients, vitamins and minerals. The National Cholesterol Education Program guidelines provide a framework for designing an individualized diet. The Step I diet recommends a diet that provides less than 30% of calories from fat. The saturated fat should compose no more than 8 - 10 % of total calories. (29) An example of the approximate dietary composition of a

recommended weight loss diet is shown in Figure 4. Putting numbers with these percentages can be helpful when comparing the standard diet with a popular diet. For example, a woman who is on a 1200 calorie diet will have 165 grams of carbohydrates, 45 grams of protein and 40 grams of fat. The amount of protein is adjusted to equal about 0.8 g/kg per day. Athletes require approximately 1.0 g/kg protein per day.

Table 2: Characteristics of an Ideal Weight Control Program

Weight loss of 1 to 2 lb per week (Calorie deficit of 500 -1000 kcal/day)
Behavioral modification therapy
Individualization of diet
Incorporation of physical activity
Effective long term maintenance of weight loss

An ideal weight control program addresses behavioral modification, psychosocial support and appropriate levels of physical activity. The program should be safe, provide a match between the consumer and the program and have established efficacy.(30) For example, if a patient has a small amount of weight to lose, a VLCD would be inappropriate. Outcomes data $\geq$ 1 year after treatment should be available and show successful maintenance of weight loss. The program should be amenable to individual preferences in order to maximize compliance. (31) The rate of weight loss should be 1-2 lb per week. A weight loss of 10% over six months is a reasonable goal to decrease the severity of co-morbid illnesses caused by obesity. This degree of weight loss is also attainable. (32) (Table 2) After six months, the patient will require either a continued weight loss plan or a maintenance plan depending on whether they have achieved health related and/or personal goals.

After the successful completion of a weight loss program, maintenance of weight loss remains frustrating. The recidivism rate for weight reduction therapy is very high. Over 70% of patients who initially successfully lose weight with a low calorie diet regain at least half of this weight within two years of stopping the diet. (33) Exercise is an important contributor to long term weight control. Continued follow up and behavioral therapy with a provider also seem to aid in weight maintenance.

Pharmacologic and surgical therapy should be reserved for patients with a BMI $\geq$ 30 or those with a BMI of $\geq$ 27 with obesity associated co-morbidities who have failed to lose the recommended amount of weight after six months. There are two drugs that are FDA approved for long term use in weight reduction: sibutramine and orlistat.

The first drug currently approved for weight reduction is sibutramine (Meridia ®). This drug was initially developed for use as an antidepressant and acts as a norepinephrine, dopamine and serotonin reuptake inhibitor. It also acts as an appetite suppressant. This drug appears to be effective for maintaining weight loss for up to one year. Weight loss is dose responsive and may be up to 5% at 1 year following a very low calorie diet.(34) One study demonstrated a 12.1 lb weight loss at one year with sibutramine. (35) The starting dose of this medicine is 10 mg and may be increased after four weeks to 15 mg per day. Adverse effects include tachycardia and elevated blood pressure as well as dry mouth, headache, insomnia and constipation. (36)

Orlistat (Xenical ®) is the other FDA approved medication for weight reduction. Orlistat is an intestinal lipase inhibitor that decreases absorption of dietary fat by 30%. It is given at a dose of 120 mg three times a day with meals. A two-year placebo controlled trial demonstrated significant weight reduction in the treatment group compared to placebo. During the first year, the

average weight loss was 10.2% compared to 6.1%. During the second year, subjects in the orlistat group regained half as much weight as placebo subjects. Thus, orlistat was effective in achieving weight reduction and weight maintenance. After two years, 57% of patients on Orlistat maintained a weight loss of greater than 5% as compared to 37% in the placebo group. (37) Adverse effects from orlistat include soft stools and decreased absorption of fat soluble vitamins. A multivitamin supplement should be given to patients taking orlistat.

Surgical therapy is reserved for a very carefully selected group of patients. These patients have clinically severe obesity (BMI $\geq$ 40 or BMI $\geq$ 35) with life threatening co-morbid conditions and have failed standard diet and exercise therapy. In these patients the risk of obesity related complications outweigh the risks of these surgeries. Therapy with banding gastroplasty along with dietary therapy resulted in higher net weight loss over a two-year period than diet alone. (38) It should be stressed that weight-reducing diets should be used in conjunction with gastroplasty to maintain weight loss after surgery.

III. THE SPIN

A. INTRODUCTION TO FAD DIETS

Although standard weight reduction therapies result in modest amounts of weight reduction, they require a great deal of discipline and major changes to lifestyle and eating behaviors. The high recidivism rate is frustrating for both patients and health care providers. The apparent failure of conventional weight reduction programs has resulted in the appearance of a large number of alternative diets.

Patients' motivations for following popular diets generally extend beyond the need for health benefits. Many patients choose a popular diet in pursuit of an improved sense of well being or in order to attain a physical ideal. A survey conducted in college women in 1985 by Arrington and Bonner listed reasons for pursuing weight reduction. Not surprisingly, 75% listed figure improvement as the most common reason and 23% listed health benefits as the reason for weight reduction. (37) Many of these diets may also be consumed by athletes who are attempting to achieve a legal "competitive edge" through the manipulation of food intake.

There are a number of other factors that contribute to the pervasiveness of popular diets. (Table 3) As a testament to their popularity and aggressive marketing, there are over 2,000 diet books available. (39) Many of these top the bestseller's lists week after week. The popularity of fad diets is fueled by a number of factors. Fad diets offer attractive claims which appeal to

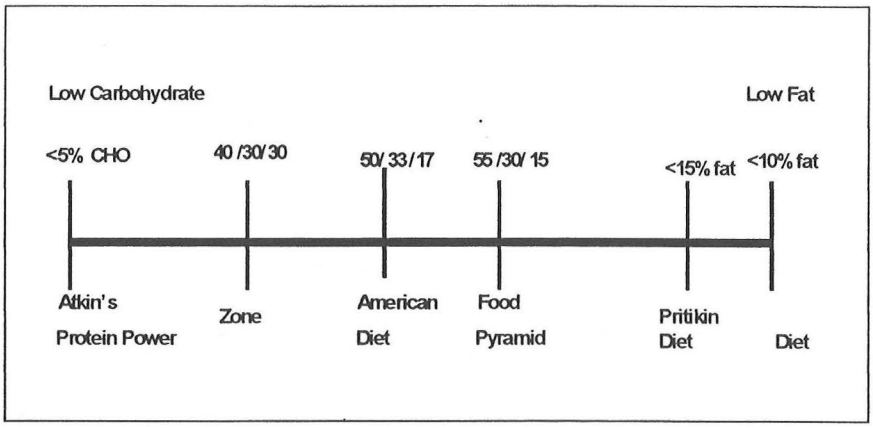
Table 3: Factors Contributing to Nutritional Fads

Failure of conventional diets
Mass marketing of popular diets and supplements
Disillusionment with "conventional medicine"
Consumer interest in "alternative" health
Promises of fad diets
Anecdotal success
Inadequate nutrition education

patients: 1) rapid weight loss; 2) easy weight loss; 3) no restriction on amount of food; 4) potential to cure various diseases. In addition, there is a perception that health care providers have an inadequate knowledge of nutrition. Most physicians do not serve as nutrition educators for patients and thus do not provide concrete, structured dietary advice for patients. There has been limited incorporation of nutrition education into standard medical school curricula. (40) (41)

Fad diets commonly fall into three categories. The first type of popular diets is the elimination diet. This type of diet "blames" one class of food as the cause of obesity and bans this food from the diet. An example of this type of diet is the Sugar Busters!` diet which states that sugar and "sugar producing" foods (potatoes, bread, etc) are the culprits behind obesity. Another example is the Dean Ornish diet which bans fat containing foods from the diet. The second type of popular diet is one that ascribes special weight losing properties to a particular food. Examples of this diet include the grapefruit diet and the cabbage soup diet. The third type of popular diet is that which is followed as an expression of a life style. An example of this is the Zen Macrobiotic diet. This diet maintains that the consumption of grains and brown rice is a way to achieve a state of enlightenment.

Figure 5: Spectrum of Popular Diets (Modified from (42)



Typical popular diets fall into a spectrum from extremely low fat to extremely low carbohydrate (Figure 5). The popularity of fad diets waxes and wanes in part because of the rapid weight loss initially achieved, followed by weight regain. During this period of weight regain, patients may try a novel diet that again induces rapid weight loss.

The current "rage" in diets is the low carbohydrate diet. These types of diets are not new and actually have a long history of cyclic popularity. Greek Olympians utilized high meat, low vegetable diets over 2000 years ago to improve athletic performance. A low carbohydrate diet was described in 1872 by English surgeon Dr.William Harvey in order to induce weight loss. (43) Dr. Harvey's diet prohibited sweet and starchy foods and permitted the *ad lib* consumption of meats. These diets regained popularity in the late 60's and early 70's with the publication of the Dr. Atkins' Diet Revolution, Stillman's Diet, The Drinking Man's Diet, the Scarsdale diet and the Air Force Diet. The AMA and other medical organizations strongly criticized these diets and the diets gradually fell out of favor. (44) Over the past decade, low carbohydrate diets have once again gained popularity. Celebrities such as Oprah Winfrey, Jennifer Aniston, Kenny Rogers and Suzanne Somers have helped boost the low carbohydrate diet craze. The Oprah Winfrey show has devoted four shows to date on the Carbohydrate Addicts Diet book which touts the benefits of this diet for people for whom, "eating certain foods is (like) doing drugs for drug addicts."(45)

Low carbohydrate diets theorize that high carbohydrate intake rather than high fat intake is the actual etiology of obesity through hyperinsulinemia. I will review two popular weight loss diets

(Atkins' diet and The Zone) that serve as examples of low carbohydrate diets and demonstrate some of the common characteristics of current popular diets.

B. DR. ATKINS' NEW DIET REVOLUTION

Dr. Atkins' New Diet Revolution is authored by Manhattan cardiologist, Dr. Robert C. Atkins. It is a modification of his original diet written in 1972. In the six years since its publication, more than 5 million copies have been sold. The diet revolution he refers to is the use of ketosis to initiate and maintain weight loss. His book theorizes that "almost all obesity exists for metabolic reasons." (46), p. 6. His diet book is peppered with anecdotes, recipes, diet information, reports of success, criticism of the medical community and scientific references. His diet is based on metabolic studies done in the 1950's by British researchers Kekwick and Pawan. (47) This study was performed in 14 "definitely" obese subjects who were fed 1000 calorie diets consisting of either 90% fat, protein or carbohydrates for 5 to 9 days. It is noted that compliance was a problem in the study, but specific data on compliance and dropouts and numbers actually analyzed are not included. Results are reported as "...selected, a considerable number of known failures in discipline being discarded." The results of this study demonstrated weight loss on the high protein and high fat diets and weight maintenance or weight gain on the high carbohydrate diet. Despite numerous potential confounding variables and methodological problems with this short term study, it is the basis of Dr. Atkins' diet book. Dr. Atkins further expounds upon the presence of a "fat mobilizing substance" that was isolated in rats in 1960. (48) This substance was isolated from rat urine and when injected into other rats resulted in hypoglycemia, ketonemia, hyperlipidemia, fatty liver, increased fat catabolism and weight loss. Dr. Atkins reports that this is the substance that confers the "metabolic edge" that causes weight loss in his diet.

From these studies, Dr. Atkins puts forth the following as his theory of obesity: excessive carbohydrate consumption results in hyperglycemia which results in hyperinsulinemia which results in the deposition of fat. His solution to this is the diet mediated reduction of insulin. By reducing the amount of carbohydrates in the diet, the "fat mobilizing substance" is activated and produces ketosis. He spends one chapter discussing the benefits of what he terms "benign dietary ketosis." He states that "Ketosis is one of life's charmed gifts. It's as delightful as sex and sunshine, and it has fewer drawbacks than either of them." (46), p. 58. Ketosis is the goal of his diet and he proposes that it is obtained by following a severely carbohydrate restricted diet. The promises of his diet are summarized in Table 4.

Table 4 : Promises of the Atkins' Diet

Eat unlimited quantities of food without hunger
Steady weight loss
Improves overweight associated health problems
Cure diet related disorders (hypoglycemia, systemic yeast syndrome, food intolerance)

His weight loss program consists of four separate diets that progress from severe carbohydrate restriction to more liberal carbohydrate consumption: induction to ongoing weight loss to pre-maintenance and then to the maintenance diet. The first phase of the diet is the "induction diet." During this phase of the program, the amount of carbohydrates is restricted to 20 grams per day. This is equivalent to about three cups of salad greens a day. Breads, pastas, soft drinks, fruit,

starchy vegetables and dairy products (other than cheese, cream or butter) are prohibited. There are no restrictions on the amount of pure proteins or fat consumed. He provides the following sample menu for the induction diet:

Breakfast: 2 scrambled eggs; 1 cup decaffeinated coffee or tea Lunch: 1 bacon cheeseburger, no bun. 1.5 cups salad greens; 1 cup of water Dinner: 1 cup shrimp cocktail with mustard and mayo; 8 oz steak; 1 cup clear broth; 1.5 cups salad greens; 1 cup diet jello.

The induction diet is followed for 14 days. Once this is complete, the subject begins to add carbohydrates in 5 gram/day increments to his/her diet. This is done through the ongoing weight loss then the pre-maintenance then maintenance diets. A sample menu from the maintenance diet is shown below:

Breakfast: Gruyere and spinach omelet; ½ cantaloupe; 4 carbohydrate grams of bran crispbread with butter; decaffeinated coffee or tea Lunch: roast chicken; 2/3 cup vegetables; green salad; club soda Dinner: French onion soup; salad; 1 cup permitted vegetables; ½ small baked potato; lightly breaded veal chops; cup fresh fruit compote; dry wine.

In addition to his eating plan, he spends a chapter discussing the benefits of exercise for overall health. He also recommends a number of supplements that should be taken when following his diet program. He provides a list of approximately thirty supplements to be utilized in varying quantities for different maladies that may affect the dieter. His Atkins' Center for Complimentary Medicine provides these vitamins assimilated into special formulations. He recommends the Dieter's Formula #3 for all those following his diet. This supplement contains 31 different minerals and he recommends taking 6 – 9 per day. Additional supplements may be necessary depending on symptoms. For example, those with hypertension should take the Dieter's formula 3 and magnesium, L-taurine, Pyridoxal 5 Phospate, garlic, essential fatty acids, CoQ10, potassium or all these combined into Atkins' formula AH-3 plus essential oils formula.

It is clear from reviewing his promises and from the sample menus that the appeal of his diet rests with the apparent lack of deprivation. Furthermore, the anecdotal success results from the weight loss that is seen with this diet. The reasons for weight loss likely stem from the following factors (Table 5):

Table 5: Etiology of Weight Loss on Atkins' diet

Satiating properties of protein
Anorectic effects of ketosis
Restriction of food choices
Glycogen depletion and concomitant water loss
Ketone body diuresis

1) Caloric restriction. The high satiating properties of protein result in a self reduction in calories by subjects. In addition, ketones have an anorectic effect which may also reduce caloric intake. Finally, the limitation of food choices also reduces the number of calories consumed. The nature of this diet requires

careful attention to what is consumed and limits the consumption of frequently energy dense pre-prepared foods. For example, cereal, soft drinks, pizzas, desserts and many fast foods are restricted due to their high carbohydrate content. These foods also contain high amounts of fats and are consequently energy dense.

2) Water loss: Glycogen mobilization results in a commensurate water loss which may cause a decrease in fat free mass rather than fat mass. Each gram of glycogen is mobilized with approximately 3 - 4 grams of water. Archibald, et al reviewed the weight reducing effects of high protein diets in 17 healthy, obese adolescents. There was a reduction in total weight with 44% of the weight lost being fat free mass. (49) Ketone bodies also generate a diuresis because, as non reabsorbable anions, they increase distal sodium delivery and therefore encourages water loss.

To summarize the Atkins' diet: Dr. Atkins proposes that obesity and certain diseases are caused by hyperinsulinemia via overconsumption of carbohydrates. Since the cause of obesity is simple, he proposes a simple solution in the form of reducing carbohydrate consumption. The Atkins' diet consists of marked reduction in carbohydrate consumption with an increase in the consumption of protein and fat. The induction of ketosis is important in this diet.

C. ENTER THE ZONE

Barry Sears, Ph.D., defines the Zone as a "near euphoric state of maximal physical, mental and psychological performance" in his book entitled Enter the Zone. (50) His diet is designed not only to induce weight loss but also to improve general well being. Like other low carbohydrate diets, Dr. Sears blames the current obesity epidemic on increased carbohydrate consumption and hyperinsulinemia. He states, however, that the weight loss seen on ketogenic diets is due to loss of lean body mass rather than actual fat loss and thus recommends a more balanced approach to a diet.

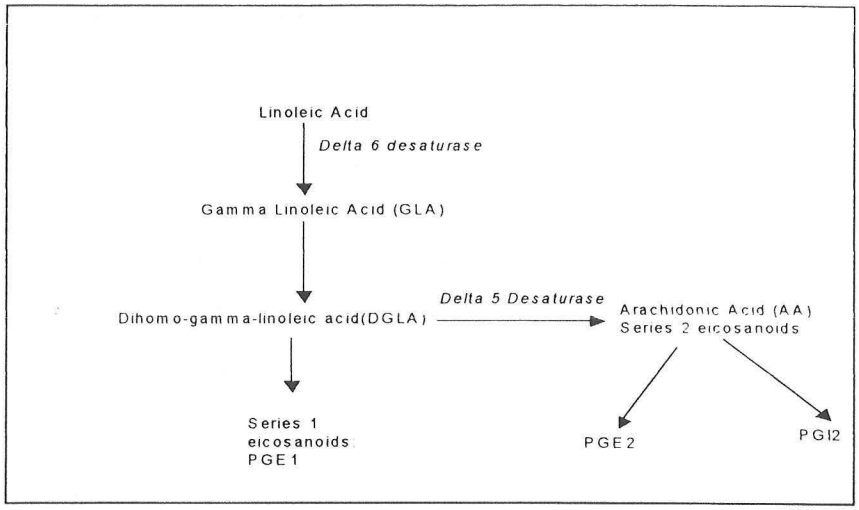
Table 6: Promises of the Zone Diet

Permanent weight loss
Reset genetic code
Prevent disease
Improve physical performance
Enhance mental productivity
Alleviate disease related symptoms

Dr. Sears promises that by following his diet, one can achieve permanent weight loss, reset the genetic code, prevent disease, improve physical performance, enhance mental productivity and alleviate symptoms from Multiple Sclerosis to HIV. (Table 6)

He also reports that his diet was responsible for the success of the Stanford swim team in the 1994 NCAA swimming championships and in the Barcelona Summer Olympics. The studies he quotes to support these assumptions are uncontrolled observational studies published in his book. He claims that his diet has cured cardiomyopathy and "kidney cancer." (50), p. 5 & 6. He reports that calories do not correlate with weight and that the cause of obesity is a diet high in carbohydrates due to increased insulin levels. The recommended "healthy" diet, he says is composed of 70% carbohydrates, 15% fat and 15% protein.

Figure 6: Simplified Pathway for Prostanoid Synthesis



His scientific background focuses largely on the hormonal regulation of weight and wellness. He reports that his dietary theories were inspired by 1982 nobel prize winners Samuelsson, Bergstrom and Vane for their pioneering work in prostaglandins and prostacyclins. From their work, Dr. Sears proposes that the Zone can be achieved by adjusting the levels of these and other eicosanoids. He explains that eicosanoids are the "master switches" of the body and thus control all bodily functions including hormones. He reports that eicosanoid levels are largely controlled by dietary factors and theorizes that controlling the dietary intake of their precursors will help achieve the Zone. As such, he considers food to be medicine. He labels eicosanoids as good or bad depending on their effects on the body. The balance of "good" and "bad" eicosanoids helps to determine whether one is or is not in the Zone. A simplified illustration of prostanoid synthesis is shown in Figure 6. Series one prostaglandins ("good" eicosanoids) are derived from dihomo-gamma-linoleic acid (DGLA) and contain a single double bond. Series two prostaglandins ("bad" prostaglandins) are derived from arachadonic acid. In order to increase the amount of series one prostaglandins, he suggests a three pronged approach: use dietary measures to increase the consumption of precursor gamma linoleic acid (GLA) for PGE1; enhance the enzymatic activity of delta 6 desaturase and inhibit the enzymatic activity of delta 5 desaturase. Since oatmeal contains high quantities of GLA, he "prescribes" 3 to 5 bowls per week. He reports that carbohydrates inhibit the activity of delta 6 desaturase and that insulin accelerates delta 5 desaturase thus limiting the formation of good eicosanoids. He states that glucagon and a high protein diet will decrease the activity of delta 5 desaturase thus reducing the formation of bad eicosanoids. Hence his dietary formula calls for reduced carbohydrates and increased protein in the diet.

The scientific literature does show that dietary factors can affect the activity of enzymes involved in the prostanoid synthesis pathway. Carbohydrates seem to have an inhibitory effect on delta 6 desaturase in rats and in humans.(51), (52), (53) However, insulin appears to stimulate both delta 6 desaturase and delta 5 desaturase activity and glucagon inhibits both delta 5 and delta 6 activity.(53) This would result in a neutral effect on prostaglandin synthesis. The dietary and hormonal regulation of series 1 and series 2 prostaglandins is complex and is only rudimentarily understood.

The Zone diet itself is complex and requires significant planning and attention to detail. It consists of a moderate restriction of carbohydrates to provide 40% of the total calories. Fat is to provide 30% of total calories and protein the remaining 30% of calories. It is therefore considered a 40/30/30 diet. The diet begins with a calculation of individual protein requirements. These

protein requirements are converted into "blocks." One protein block equals 7 g protein; one carbohydrate block is equal to 9 g carbohydrates and one fat block is equal to 1 1/2 grams of fat. Each meal is divided into "protein blocks" consisting of a certain number of protein blocks, carbohydrate blocks and fat blocks depending on the individual's protein requirements. Carbohydrates are designated as favorable or unfavorable based largely upon their glycemic indices. Those carbohydrates that have a high glycemic index induce a rapid rise in insulin secretion and are therefore considered unfavorable; low glycemic index carbohydrates cause a more gradual rise in insulin levels. Each meal should have a ratio of 1:1:1 in protein: carbohydrate: fat blocks. Each day is broken into 3 meals and 2 snacks. Each meal is to be no more than 500 calories and each snack is to be no more than 100 calories. Meals should be precisely spaced apart in order to prevent good eicosanoid levels from "dropping out" of the Zone. Those who require higher amounts of protein are advised to eat more meals. Exercise is stressed as an important way to stay in the Zone. (50)

The Zone diet stresses low fat protein sources and the dietary composition is closer to recommended levels. 30% of calories from protein may be difficult to achieve, however. Exercise is emphasized as an important adjunct to dietary therapy to achieve the Zone. The calorie content of the diet is low and will result in weight reduction for some individuals based on caloric restriction alone. It is a complex diet that requires the dieter to precisely measure their intake and plan their meals completely. Attention to the quality of food intake may help to minimize caloric intake.

This diet has been very attractive to athletes and young people. Elite athletes are particularly charmed by Dr. Sears' promises of improved performance and a "competitive edge." Since athletes utilize these diets, some mention should be made about the utility of this diet for athletic performance. Carbohydrate loading has been a popular technique for endurance exercise. It involves depleting the body of glycogen stores completely approximately six to seven days before the endurance event. A high fat, high protein, low carbohydrate diet is followed for approximately three days. Approximately 100 gm of carbohydrates is recommended during this phase. The next phase of carbohydrate loading involves obtaining the majority of calories from carbohydrates. Exercise is not recommended during this phase in order to store the maximal amount of glycogen possible. On the day of the event, the athlete is allowed to eat anything they wish about 4 to 6 hours before the event. (54). These diets are recommended because high carbohydrate diets correlate with increased glycogen stores, which in turn correlate with improved performance in endurance events. (55) Short-term activities such as sprinting would not benefit from carbohydrate loading.

To summarize the Zone diet: this diet seeks to improve wellness by manipulating eicosanoid levels. This goal is achieved by treating food as medicine and taking appropriate "doses" of protein, carbohydrates and fats at specifically designated times.

IV. THE SCIENCE

The Atkins' diet is the prototype of the low carbohydrate diet. The Sugar Busters' diet, Carbohydrate Addicts diet, Protein Power diet and the Zone diet are all variations on the low carbohydrate diet theme. These diets alter the macronutrient content of diets to favor protein and some advocate ketosis to induce weight loss. They are variable in their recommendations for dietary fat content. The Zone diet recommends a diet with 30% fat that is congruous with NCEP recommendations. The Atkins' diet places no restriction on fat consumption. The area of greatest

controversy is the nutritional adequacy of popular diets. The food guide pyramid was developed to provide a simple representation of nutritional guidelines. (56) These guidelines are designed to provide the recommended daily allowances of vitamins, minerals and macronutrients. Comparing the current popular diets with the food pyramid guide reveals the absence or diminishment of a number of large food groups suggesting the possibility for nutritional inadequacies. (Figure 7A and 7B).

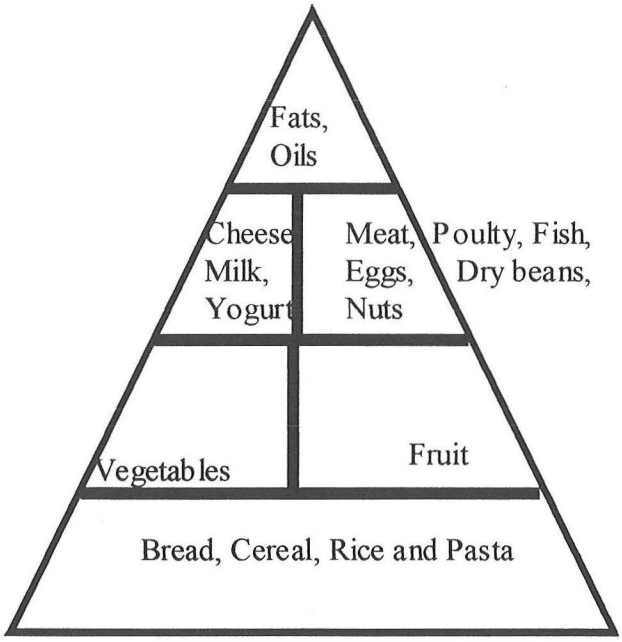


Figure 7A: Food Guide Pyramid

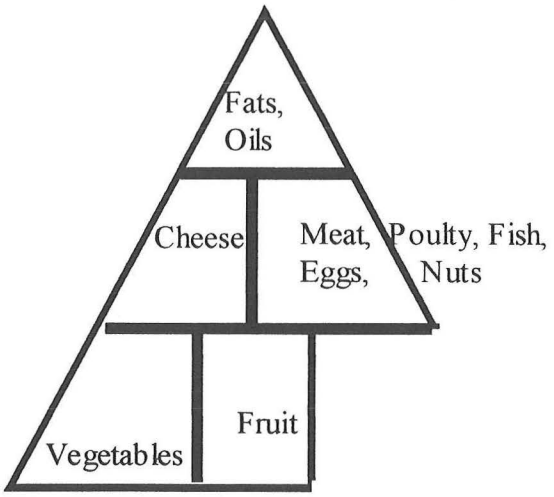


Figure 7B: Low Carbohydrate Diet "Pyramid"

There is little in the scientific literature that specifically examines each individual diet. The efficacy and side effects of these diets must therefore be inferred from studies reviewing various aspects of these diets. Each component of the diets (ketogenicity, low carbohydrate content and high protein content) can be considered in turn.

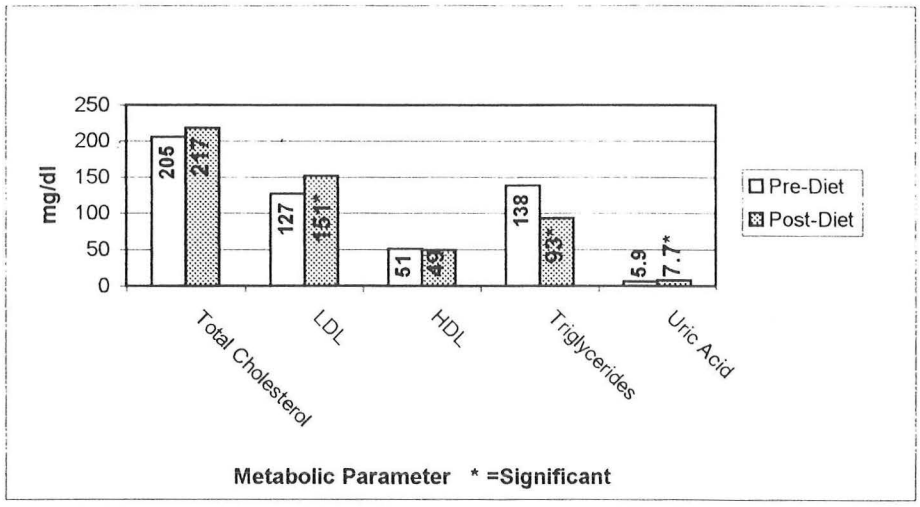
A. METABOLIC EFFECTS OF KETOGENIC DIETS

Ketogenic diets have been used for decades in epileptic children with refractory seizure disorders. Ketosis is induced by a high fat, low carbohydrate diet and appears to be an effective treatment for these children. The exact mechanism of prevention of seizures by these diets is disputed. Studies in the brains of mice show that ketosis results in raising the seizure threshold by increasing ATP concentrations. Metabolic studies utilizing these diets can be used to evaluate potential side effects of other ketogenic diets such as the Atkins' diet. These studies have shown an increased incidence of kidney stones. (57) Other studies have demonstrated the presence of constipation, dehydration, inadequate intake of calcium, magnesium and iron. Less common adverse events include hyperlipidemia, impaired neutrophil function, optic neuropathy, osteoporosis and protein deficiency.(58) Since ketogenic diets are used to treat patients with refractory epilepsy, Wing, et al reviewed the cognitive effects of ketogenic very low energy weight reduction diets compared with non ketogenic very low energy diets. There was a decrease

in higher order mental processing and flexibility on the ketogenic diet. The amount of weight lost on the ketogenic diet was comparable to weight lost on the non ketogenic diet. (59)

Although these results suggest that the ketogenic aspects may result in some of the adverse symptoms, the ill effects of the diet may in fact be due to the high fat content of the diet. A study by Larosa, et al done in 1980 followed 24 obese subjects on an Atkins' type induction and maintenance diet. They consumed on average 534 fewer calories on the diet; 107 g of protein, 108 grams of fat and 6 grams of carbohydrate while on the study protocol. Participants lost an average of 7.7 kg on the diet over 8 weeks. This weight loss was maintained at 5.9 kg less than their pre-diet weight 1 year after the study was complete. LDL rose significantly; triglycerides dropped over the eight week period and uric acid rose significantly. (Figure 8) Symptomatic complaints were few and included fatigue, thirst, lassitude, bad taste and foul breath.

Figure 8: Larosa, et al (62): Metabolic Effects of Atkins' "Type" Diet



Hoyt and Billson reported the development of optic neuropathy in two patients following a low carbohydrate, high protein diet for 4 1/2 and 5 1/2 months, presumably due to diet induced thiamine deficiency. (60)

B. METABOLIC EFFECTS OF HIGH PROTEIN DIETS

Other studies have incorporated higher percentages of carbohydrates than is allowed on the Atkins' diet. These studies have predominantly focused on the effects of high protein diets on mineral metabolism and bone homeostasis. The results are summarized below in Table 7.

Table 7 : The Effects of High Protein Diets on Urinary Parameters

Reference	Urine Calcium	Urine pH	Urine Uric Acid	GFR
Fellstrom(61)	↑			
Larosa(62)				
Schuett (63)	↑	↓		↑
Licata(64)	↑	↓		↑
Licata(65)	↑	↓		
Kok(66)	↑	↓	↑	
Fellstrom(67)		↓	↑	↑
Pannemans(68)	↑			
Kerstetter(69)	↑	↓	↑	
Licata(70)	↑	↓		
Anand(71)	↑			
Kim(72)	↑			↑
Robertson(73)	↑		↑	

These studies demonstrate that increasing the protein content of a diet while controlling other metabolic parameters results in increased GFR, increased urinary calcium excretion, increased titratable acid excretion, decreased urinary pH and increased urinary uric acid excretion as well as increased serum uric acid. The mechanism of increased urinary calcium excretion is purported to be the increased acid load conferred by a high protein diet. This high acid load results in a subclinical chronic metabolic acidosis causing bone resorption with calcium mobilization. (74) Osteoclasts and osteoblasts respond to small changes in pH in cell culture; thus, a small decrease in pH results in a large burst of bone resorption. (75) These effects may be exaggerated in elderly patients who tend to have decreased renal ability to excrete acid and have elevated serum PTH concentrations.(74). Kerstetter et al reviewed bone turnover in young women consuming varying levels of dietary protein. They found increased renal calcium excretion, secondary hyperparathyroidism and elevated urinary N-telopeptide in those consuming a low carbohydrate diet. Markers of bone formation (alkaline phosphatase and osteocalcin) remained steady suggesting increased bone resorption without an increase in bone formation. (76)

Table 8: Metabolic Sequela of High Protein Diets

Hyperuricemia
Hyperuricosuria
Hypercalcuria
Hyperaciduria
Hypocitraturia
Possible osteopenia

There also appears to be an increase in the glomerular filtration rate as well as a decrease in renal tubular reabsorption of calcium. In addition, a diet high in animal protein decreases gastrointestinal alkali absorption which ultimately results in decreased urinary citrate. (77) Hypercalciuria, hyperuricemia and hypocitraturia induced by high protein diets can all contribute to renal calculi formation, gout and potential decrease in bone density. (Table 8) There is substantial evidence that dietary protein restriction is important in retarding the progression

from diabetic nephropathy to end stage renal disease; a high protein diet would thus be deleterious to this group of patients.(78)

C. LOW CARBOHYDRATE DIET STUDIES

There are a few of studies examining normal and obese non-diabetic individuals placed on low carbohydrate diets. These studies primarily examine low carbohydrate diets in comparison to low fat diets. The results of these studies are summarized in Table 9. Results are mixed with respect to the amount of weight loss conferred by each diet. Inpatient and outpatient studies comparing hypocaloric low fat versus hypocaloric low carbohydrate diets show that the high fat, low carbohydrate diets are associated with equal or greater weight loss than the low fat, high carbohydrate diets. These results must be interpreted with caution because the studies did not measure water loss associated with glycogen mobilization in the low carbohydrate diets. In addition, most outpatient studies did not account for possible confounding variables such as exercise and diet compliance. (17) The low carbohydrate diets were generally well tolerated, with the exception of a diet with virtually no carbohydrates (2% of calories) composed of large quantities of animal protein. Compliance with this diet was extremely poor with patients stopping the diet after only 7.6 days. (79)

Table 9 : Weight Effects of Low Carbohydrate Diets vs. Low Fat Diets

Reference	*n*	Control Diet (CHO/fat/protein)	Intervention diet (CHO/fat/protein)	Total calories	Duration	Weight Change (Control vs. Intervention)
Rabast (80)	21	70/**12**/18	12/**70**/18	Hypocaloric	28 days	9.5 kg vs 11.4 kg *
Davie (81)	17	54/**12**/32	18/**50**/32	650 Kcal	17 days	No significant difference
Rabast (82)	73	70/**10**/19	10/**71**/19	Hypocaloric	30 days	9.8 kg vs. 11.7 kg*
Golay (83)	43	45/**26**/29	15/**53**/32	1000 Kcal	6 weeks	No significant difference
Golay (84)	68	45/**26**/29	25/**45**/30	1200 Kcal	12 weeks	No significant difference
Pilkington (85)	9	78/**9**/13	23/**62**/15	800 Kcal	18-24 days	No significant difference
Yudkin ((86))	6	Ad lib diet	50 g CHO	Hypocaloric	2 weeks	No significant difference
Kasper (87)	3	57% fat	87% fat	1700 Kcal	24 - 27 days	0.09 vs 0.36 kg/day*
Lewis (88)	10	70/10/20	10/70/20	10 Kcal/kg	14 days	4.4 vs. 5.2 kg*
Piatti (89)	25	60/20/20	20/60/20	800 Kcal	3 weeks	No significant difference
Baron (90)	135	50 g CHO per day	30 g Fat/day	1000 Kcal	3 months	3.7 kg vs 5.0 kg *
Alford (91)	35	75/10/15	45/35/20	1200	10 weeks	4.8 vs 5.6 kg *
Rumpler (92)	8	64/20/14	46/40/14	50%	4 weeks	No significant difference
Powell (93)	35	10% fat vs. 20% fat	40% fat	1200 Kcal	12 weeks	No significant difference
Racette (94)	23	60/**15**/25	25/**50**/25	Hypocaloric	12 weeks	8.1 kg vs 10.6 kg *
Low (95)	17	70% CHO	70% Fat	Hypocaloric	6 weeks	No significant difference
Anderson (96)	6	62/**23**/13	26/**23**/51	2000 cal	5 days	No significant difference
Rickman ((79)	12	None	2/48/50	1400-1500	7.6 days	No significant difference

D. SUMMARY OF SCIENTIFIC DATA

The available literature is mixed with regards to the weight-losing properties of high protein/low carbohydrate diets. Limited studies report increased weight loss at the start of the diet possibly due to increased loss of fat free mass (glycogen and water). The diets are generally well tolerated with minimal subjective complaints. Lipid status is generally favorably affected in the short term perhaps from overall weight reduction. Long-term data is limited with regards to metabolic effects and weight maintaining effects. The literature suggests that metabolic derangements on high protein diets include elevated serum acid load, elevated uric acid, hypercalciuria, hyperuricosuria and hypocitraturia. The clinical ramifications of these abnormalities include the potential for nephrolithiasis and osteopenia. High protein diets may hasten progression to renal failure in diabetic patients with nephropathy.

V. CONCLUSIONS

The pathogenesis of obesity is complex and multifactorial with important contributions from genetics, the environment and individual behavior. Elucidating each aspect of the intricate interaction between these factors remains a daunting task for scientists. As with any disease with a puzzling and complicated pathogenesis, treatment remains largely unsatisfactory. Standard therapy is effective if the patients can be compliant with long term diet, exercise and behavioral therapy. Until therapy for obesity becomes facile, patients will turn to popular weight reduction diets to induce rapid and easy weight reduction. The true challenge is not rapid weight reduction but long term maintenance of weight loss.

There is insufficient evidence in the literature to support claims by low carbohydrate, high protein diets that the substitution of protein for carbohydrates is superior for affecting long-term weight loss. The so-called short term weight reduction "advantages" of such diets may be due to glycogen mobilization and concomitant obligatory water loss. In addition, by restricting dietary choices, elimination diets likely result in overall reduced caloric consumption. The long-term serum effects of the high fat content of some of the current popular diets is largely unknown. These diets also have the potential for vitamin and nutritional deficiencies due to the restriction of large categories of food. Low carbohydrate diets may also contain low levels of antioxidants. The low fiber content of many of the diets can result in constipation. Long term effects of reduced dietary fiber may include an increased risk for colon cancer. Although the high protein content of the diets results in improved satiety, the restriction of a large category of macronutrients (e.g. carbohydrates) makes long term maintenance of weight loss challenging. While ketosis does result in anorexia and appetite suppression, the sub-clinical acidosis induced by such diets may result in nephrolithiasis and long term bone loss. Elevated uric acid levels can result in a gouty diathesis. High protein, low carbohydrate diets are not appropriate for pregnant women or for patients with renal disease. The initial diuretic effects of the ketone bodies and glycogen mobilization may result in orthostasis in patients who are taking diuretics.

The advantages to popular weight reducing diets lie in the structure that is provided to patients. They provide patients with concrete information on what can and cannot be eaten. In addition, many popular weight-reducing diets emphasize exercise. They all suggest some form of behavioral modification although some of the recommended behaviors (restricting carbohydrates) may be difficult to maintain long term. These diets provide an increased awareness of foods consumed and thus may also limit the amount consumed. The Sugarbusters! diet and the Zone

diet, for example, discuss the importance of low fat sources of protein and some diets recommend a diet with macronutrient compositions close to recommended levels.

Physicians should take an active role in counseling patients about obesity, diet and exercise. When a patient asks about popular weight reducing methods, they are prepared to lose weight. This is a prime opportunity to provide them with resources and advice on standard weight reduction techniques. A reputable registered dietician is an invaluable resource at this time. Counseling to prevent obesity should also be an important component of the routine health evaluation. Randomized studies should be performed to evaluate the long-term efficacy and side effects of low carbohydrate, high protein diets. Finally, nutrition education in medical school curricula must be improved so physicians can provide patients with clear information about diet.

VI. PATIENT ADVICE

Many popular diets typically will result in short-term weight loss due to restricted food choices. Some diets also result in water loss. These diets may be difficult to maintain long-term because of limited selections of food. Restrictive diets may cause nutritional deficiencies. High protein, low carbohydrate diets can result in kidney stones, gout or long term bone loss. The cosmetic advantages to weight reduction by popular diets are probably outweighed by the potential risks posed by such diets. The health benefits of weight reduction can be realized with slow, gradual weight loss using a balanced diet and behavioral modification program. Dietary changes should be sustainable over the long term. Exercise is an important component of a weight reduction program for its health benefits and for weight maintenance. The following are resources that can be given to patients:

- www.nhlbi.nih.gov/nhlbi/cardio/obes/summary (national guidelines, a BMI calculator and weight loss tip sheets)
- www.eatright.org (The American Dietetic Association).
- www.wheatfoods.org (slide show on fad diets)
- Dieting for Dummies Kirby, Jane.

Acknowlegements: many thanks to Abhimanyu Garg, M.D.; Chia-Ying Wang, M.D.; J. Denis McGarry, Ph.D.; Margo Denke, M.D.; JoAnn Carson, R.D., M.S..; Linda Moncrief; Margaret (Peg) Kelly; T.A. Reddy, M.D.

National Heart, Lung, and Blood Institute (2)

Body Mass Index Chart

Height (inches)	Body Weight (pounds)																
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

Body Mass Index Table

Height (inches)	Body Weight (pounds)																		
	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
58	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

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