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– Review –

Macronutrient Intake and Obesity

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Abstract

Obesity is a global pandemic that is increasing throughout most of the world. Increases in obesity are not restricted to highly industrialized countries, but have been observed in newly developed and developing countries as well. Obesity is associated with increased risk for non-insulin dependent diabetes mellitus, coronary artery disease, and some types of cancer. Tragically, eliminating food shortages in developing countries may result in substituting heart disease, diabetes, and cancer for malnutrition. There are many approaches to reducing obesity, including dietary modification, surgical interventions, and drug therapies. However, only dietary modification has the potential to be effective on a global scale. Public health measures in the United States have sought to reduce obesity by reducing the intake of dietary fat. While these efforts have succeeded in reducing dietary fat, obesity has continued to increase, suggesting that moderate fat reduction may not be effective. Other proposed diets include low-carbohydrate diets, low glycemic index diets, and very low fat diets. While all of these diets may be effective for some people, they are not satisfactory for public health policy. In fact, the ratio of fat to carbohydrate may not be as important as previously believed. Humans may be well suited to adapt to diets as varied as a high carbohydrate tropical diet consisting mostly of fruits to the high fat Eskimo diet consisting largely of animal foods. Either extreme may be healthful if providing adequate, but not excessive, energy and adequate amounts of micronutrients. Public health measures may need to focus on reducing the overconsumption of inexpensive and convenient foods.

Key words: obesity, fat, carbohydrate

INTRODUCTION

Obesity and obesity related disease is a cause of significant mortality and morbidity in much of the world. In the United States of America (USA) obesity has reached epidemic proportions. The accepted standard for determination of obesity and overweight is the body mass index (BMI). Accepted interpretations of BMI are shown in Table 1 (1). Recent evidence suggests that approximately 50% of adult Americans are overweight or obese as defined by a BMI ≥ 25 (2-4). The National Health and Nutrition Examination Surveys (NHANES) show that the incidence of obesity (BMI ≥ 30) among adults increased from 14.5% in the 1976 ~ 1980 survey years to 22.5% in the 1988 ~ 1994 years (5). Recent telephone survey data from the Centers for Disease Control (Atlanta, GA) suggests that obesity continues to rise in the United States (2). Although obesity has been of serious concern and considerable research in the United States, increases in obesity are a worldwide trend. In fact, many people believe that obesity has reached the status of a global pandemic (1). Even developing countries attempting to solve problems of chronic energy deficiency are experiencing a concurrent increase in the incidence of obesity, and morbidity associated with both undernutrition and overnutrition occurs within the same population. Mexico is

Table 1. Body Mass Index (BMI) standards and definitions (1)

BMI < 18.5: Underweight, indicates chronic energy deficiency
BMI 18.5 ~ 24.99: Normal
BMI ≥ 25 ~ 29.99: Overweight grade Ⅰ
BMI > 30.00 ~ 39.99: Overweight grade Ⅱ
BMI > 40: Overweight grade Ⅲ

The above definitions are not universally used and careful attention must be used in reading research in which BMI (weight in kg/height in m^2) data is presented to ascertain what definitions are used for determining overweight and obesity. Many authors combine overweight grades Ⅱ and Ⅲ and refer to those grades as obesity rather than overweight.

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a lower income country in which obesity has reached similar proportions to the USA with>50% of the population overweight (6,7). Brazil, Peru, and Columbia reportedly have escalating rates of obesity as well, although data is limited (8-10). On the whole, Asian countries still have a comparatively low incidence of obesity. However, when countries have data available for urban versus rural populations, there is often a high incidence of obesity in the urban areas. This has been demonstrated in Thailand, Malaysia, and China (6,11,12), with urban China apparently having one of the most rapidly increasing incidences of obesity in the world.

Obesity is much more than just an inconvenience or cosmetically undesirable physical trait. Obesity should be considered a serious disease. It has been estimated, based on data from several large population studies, that in 1991 there were 280,000 deaths in the USA that were attributable to obesity. About 80% of those deaths were in people with a BMI>30 (13). Increasing comorbidity with obesity has been shown for non-insulin dependent diabetes mellitus (NIDDM), coronary heart disease, high serum cholesterol, high blood pressure, and osteoarthritis (14). Obesity is also a risk factor for colon cancer and overall mortality (15,16). Obesity risks may not be the same for all populations, however. Korean NIDDM patients tend to have less obesity than do Caucasians and blacks (17). Whether the difference between populations is a result of a different type of NIDDM, fat deposition between populations or other factors is not clear. Although, in that study a smaller percentage of the NIDDM patients were obese, it was not determined if a smaller percentage of obese Koreans are NIDDM, therefore, obese Koreans may be at as great a risk for NIDDM as other ethnic groups.

The increased incidence of obesity has been the subject of great concern. A recent survey found that 28.8% of men and 43.6% women age 18 and over in the USA are attempting to lose weight (18). Weight loss strategies include surgical interventions, drug therapies, exercise, and dietary modifications. The focus of this review is on dietary modifications and specifically on manipulations of macronutrients (fat, protein, and carbohydrate). Four very different approaches to weight loss will be compared. Each approach has been recommended by reputable scientists and/or physicians, resulting in some confusion about which dietary approach is most effective and healthful. The most common recommendation in the USA is to reduce dietary fat (to 30% total energy) and increase dietary carbohydrates. Severe reduction of dietary fat to less than 10% of energy intake has also been suggested as a cure for obesity and heart disease. An opposite approach that will be reviewed is the low carbohydrate (ketogenic) diet. Finally, a low glycemic index diet will be reviewed. This diet avoids foods that are high on the glycemic index, but may have a varied content of carbohydrate and fat.

Consideration of altering the energy substrate concentration of foods for the purpose of weight loss or gain has substantial practicality. Altering the behavior of individuals is difficult on a global scale. However, altering the energy content of available foods by encouraging production of foods with a desirable macronutrient profile is possible. It is important, however, that sweeping changes in global food supply be approached with extreme caution and excellent science.

REDUCED FAT DIET

In 1977 the United States Senate's "Select Committee on Nutrition and Health Needs" issued the bulletin, *Dietary Goals for the United States*, which recommended that Americans reduce dietary fat to no more than 30% of total energy (19). There was a significant consensus among scientists, at the time, that the high fat content of Western diets was responsible for the high incidence of obesity in most industrialized nations. Epidemiological surveys demonstrated that populations with a high fat diet had a higher incidence of obesity. Data from immigrant populations suggested that genetic differences, between the different ethnic populations, was not responsible for the epidemiological observations. For instance, Japanese men living in San Francisco had a threefold higher incidence of obesity than Japanese men living in Japan (20). It makes sense that dietary fat would contribute more to obesity than other energy nutrients. Fat provides approximately 38 kJ/g of energy, while protein and carbohydrate provides closer to 17 kJ/g. If food consumption is regulated by the volume of food eaten, a diet high in fat would be more energy dense and therefore lend itself to a higher consumption of total energy. Furthermore, about 25% of the energy of carbohydrate is expended in its conversion to fat (21), whereas very little energy is required for the storage of dietary fat in adipose tissue.

Unfortunately, however, reducing the incidence of obesity appears more complex than simply reducing the fat content of diets. Although the dietary goal of reducing the fat content of the American diet was largely successful, the increasing rate of obesity was refractory to the change. In the USA, total dietary fat decreased from the early 1970's to 1991, but during the same time period there was a sharp increase in the prevalence of obesity (22,23). Reducing dietary fat in the population did not decrease the incidence of obesity, but instead was associated with an apparent increase in obesity.

It is important to note that the epidemiological evidence for the relationship of high fat diets and obesity was cross-sectional in nature. There was very little direct evidence that changes in the fat intake in the same population would translate into changes in body composition. The conscious effort of Americans to reduce dietary fat separated the issue of high fat diet from other issues such as affluence of the population and the easy availability of food. The American experience suggested that dietary fat was not a primary determinant of obesity in that population.

Randomized trials of individuals placed on control or reduced fat diets have demonstrated modest losses of adiposity and energy intake (24). One of the longer trials (6 months)

replaced 45 foods with low fat alternatives and reduced fat by 7% of energy (25). Body weight, however, was only reduced by 0.6 kg. Of course, if that degree of weight loss were sustained over many years it could be important. A longer-term study was the National Diet-Heart Study (26) in which the difference in fat was 30% versus 35% of energy; again there was only a small decrease in body weight of 0.8 kg. A comparison female Korean college students, eating either a vegetarian diet with 20% of energy from fat or an omnivorous diet with 25% energy from fat, found no difference in body weight between the groups (27). In the Women's Health Trial (28) dietary fat was reduced from approximately 38% of energy to 20% in the low fat group as opposed to the control group, which remained at approximately 38%. After 6 months the low fat group had lost 3.2 kg of body weight, but much of the weight had been regained by 24 months into the trial and the low fat group weighed only 1.8 kg less than the control group. This study would suggest that adopting a low fat diet results in a transient weight loss. Other intervention studies have also found that reduced fat diets have little effect on body fat or weight, even when fat was reduced below 20% of energy (29,30). Both the data from intervention trials and the inverse relationship of obesity with dietary fat in the USA are difficult to reconcile with the notion that high fat, Westernized, diets are responsible for the global obesity pandemic. Furthermore, it seems apparent that modest reductions in dietary fat are not an effective treatment for obesity in most people, and may even increase obesity in the general population.

VERY LOW FAT DIETS

Very low fat diets have been recommended for both body fat reduction and the reversal of coronary artery disease. Popularized in both scientific journals and the popular press by Dean Ornish and others, this diet is really a lifestyle incorporating a vegetarian diet with less than 10% of calories from fat, stress management, exercise, and abstinence from smoking (31-33). Subjects in these studies lost weight, however, these studies were designed to study whether the lifestyle changes could reduce coronary heart disease and were not properly controlled for weight reduction studies. The experimental group in the 1990 study (31) weighed an average of 91.1 kg at the beginning of the study and control subjects weighed 80.4 kg. After 12 months the experimental group weighed an average of 81.0 kg and the control group 81.8 kg. Therefore, following the lifestyle changes resulted in a similar weight as the control group after the 12 month study. In this study, fat intake in the experimental group was reduced from an average of 67.4 g/day (31.5% of energy) to 14 g/day (6.8% of energy), whereas initial fat intake was similar in the control group and remained the same throughout the study. Energy intake was also decreased in the experimental group (average of 8.2 MJ to 7.2 MJ per day) and exercise time increased (from 11 min/day to 38 min/day). It is likely that the decreased energy intake and increased energy expenditure, from exercise, was responsible for the loss of weight, and not the reduced percentage of fat in the diet. Similar problems exist with the 1995 study (32). However, it must be remembered that these were not weight-loss studies and the weight-loss data was a secondary aspect of the research.

Compliance may also be a problem with using the very low fat diet as a dietary modification in many societies. A 28 week study measured compliance and acceptance of an "Ornish type diet" in nine cardiac rehabilitation patients in the southeastern USA (34). Only one patient was in 100% compliance, but six were able to attain 85% compliance. The authors concluded that "motivated patients can follow a very-low-fat, near vegetarian diet", but that they need a highly structured program to do so. The motivation in that study was to avoid a second heart attack. Obtaining compliance with such a rigorous dietary program in a general population would be much more difficult, perhaps impossible.

LOW CARBOHYDRATE, KETOGENIC, DIET

Just the opposite of the "Ornish Diet" is the low carbohydrate "Atkins Diet" which has also been promoted for weight loss. Numerous books for the public have been published on weight loss diets using a low carbohydrate approach with dietary energy being primarily obtained from fat and protein (35-37). This dietary approach, at its greatest extreme, is designed to induce a state of chronic ketosis. While the safety of this diet has not been well studied for weight loss, it is essentially the same ketogenic diet that has been studied as a therapy for children with epilepsy (38,39). Children on a ketogenic diet exhibit normal growth and have no apparent ill effects as a result of the diet (40). Cognitive abilities were found to be somewhat impaired in subjects placed on a low-calorie ketogenic diet, but not in subjects on a similar non-keotgenic diet (41). Nevertheless, the ketogenic diet appears safe, however, there is still little data to support its use in weight loss programs. In the above mentioned study of cognitive effects of ketogenic diets, subjects in both groups lost similar amounts of weight during the study, so it must be assumed that the weight loss was due to the low caloric intake which was identical for both groups (41). Other studies have also used low-calorie ketogenic diets (42,43), however, the proponents of ketogenic diets claim they are effective without reducing caloric intake. Rather than providing direct clinical evidence to support very-low-carbohydrate diets for weight loss, the authors of books on the topic provide an indirect approach by establishing a hormonal basis its effectiveness. The rationale is that low carbohydrate diets elicit a minimal effect on insulin release, which favors the utilization of fat stores for energy and impedes fatty acid synthesis. While there is some validity to this line of reasoning, which will be discussed in the next section, there is little direct clinical evidence to support ketogenic weight loss diets without caloric

restriction. However, one such study has been reported in abstract form (44). Twenty-one obese adults were placed on an ad libitum low carbohydrate / high protein / high fat diet for an average of 6 weeks. During the study, all subjects lost weight with an average weight loss of 7.59±0.86 kg. Fasting insulin levels dropped by 50% in the subjects and insulin efficiency (circulating glucose:insulin ratio) increased two fold and was highly correlated with weight loss in the subjects ($r=0.703$, $p<0.001$). Unfortunately, there were no control subjects and no mention of the caloric intakes of the subjects. It is possible that the disruption of normal dietary habits resulted in a decreased caloric intake, which resulted in weight loss. Unfortunately there is still very little data to either support or refute the ketogenic diet for weight loss.

LOW GLYCEMIC INDEX DIET

A low glycemic index diet has also been proposed as a possible weight-loss diet (45). A low glycemic index diet would have the same metabolic basis as the low carbohydrate diet and possibly even the "Ornish" diet (since the "Ornish" diet eliminates sugars and favors complex carbohydrates). The glycemic index is a method of ranking foods according to their impact on blood glucose as compared to an index food such as white bread or glucose (46). Consumption of foods that are high on the glycemic index results in a high elevation of blood glucose and increased insulin response as compared to the response with foods that are lower on the glycemic index.

In the Iowa Women's Health Study, diets rich in whole grains were generally higher in energy content than diets rich in refined grains, but were associated with a lower BMI (47). The association continued even after adjusting for other whole grain components such as fiber, phytic acid, and vitamin E. It is not clear what attribute of the whole grains contributed to a lower BMI, but a lower glycemic index is certainly a possibility.

There is also good metabolic rationale to support the low glycemic index approach for weight loss. Insulin resistance and hyperinsulinemia are believed to shunt energy substrates to adipose tissue, resulting in hypertrophy and hyperplasia of adipocytes (48). Insulin is known to be a key factor in the regulation of several important enzymes that control lipid metabolism (Table 2). Fatty acid synthase (FAS) catalyzes the synthesis of long-chain fatty acids from acetyl-CoA and malonyl-CoA. Fasting, in rats, results in a decrease in FAS synthesis, whereas either refeeding or insulin treatment increases FAS synthesis (49). Lipoprotein lipase (LPL) levels in rats, like FAS, are downregulated by fasting and increased by refeeding or insulin treatment. LPL hydrolyzes circulating triacylgycerols in lipoproteins, producing free fatty acids available for uptake into adipose cells (50,51). Carnitine palmitoyltransferase-1 (CPT-1) is an enzyme which facilitates fatty acid oxidation by transporting fatty acids into the mitochondrial matrix of a cell, where oxidation occurs. CPT-1 is also

Table 2. Key regulators of lipid metabolism under glycemic control

Insulin
Insulin/Glucagon ratio
Fatty acid synthase
Lipoprotein lipase
Carnitine palmitoyltransferase
Leptin

regulated by insulin, though indirectly. CPT-1 is normally controlled by physiological concentrations of malonyl-CoA, a substrate of fatty acid biosynthesis. Higher physiological concentrations of circulation malonyl CoA reduce CPT-1 activity to very low levels. Insulin has been shown to increase the sensitivity of CPT-1 to malonyl CoA, so that relatively lower levels of malonyl CoA can virtually shut down fatty acid oxidation (52,53). Therefore, insulin can simultaneously increase the biosynthesis of fatty acids, decrease fatty acid oxidation, and increase the release of circulating fatty acids into adipose tissue; all of which would favor and increase in adiposity.

Insulin also regulates leptin, the product of the ob gene that is not properly expressed in the obese ob/ob mouse. Leptin is a hormone expressed in adipose tissue and works as a satiety factor in both humans and rodents (54-56). Studies using diazoxide, an inhibitor of glucose mediated insulin secretion, have demonstrated reduced weight gain, lower postabsorptive triacylgycerol levels in obese rats, and improved glucose tolerance in obese and non-obese rats (57,58). In a recently released study, female lean and obese Zucker rats treated with diazoxide had lower plasma triacylglycerol, free fatty acids, glucose, and insulin, as expected from previous studies (59). However, diazoxide also reduced plasma leptin concentrations in obese animals, FAS activity in adipose tissue of both lean and obese, and LPL mRNA expression in obese animals only. Less is known for certain about the effects of insulin on the mediators of lipid metabolism in humans, however insulin is known to increase FAS activity and gene transcription in cultured human adipocytes (60).

While these studies demonstrated that insulin is a promising target for pharmaceutical intervention in obese patients, it is still uncertain if a low glycemic diet would have the same effect. It is also difficult to extrapolate the results seen in an inbred strain of rats to a genetically diverse human population. The obese Zuker rat has a well defined genetic tendency for obesity that may be related to insulin metabolism, but is not necessarily analogous to human obesity. Furthermore, a possible harmful effect of chronic insulin suppression has not been studied and would need to be evaluated before such a weight loss strategy could be safely recommended.

STEMMING THE OBESITY EPIDEMIC

Despite years of research and public health measures, obesity continues to rise throughout most of the world. As the

previous sections illustrate, there is no clear message from the scientific and medical communities on what can be done to cure or prevent obesity. Until the causes of obesity are better understood, it will be very difficult to reverse, or even halt, the trend. Heritability studies, of twins reared apart, suggest that as much as 70% of the variance in human body weight may be due to genetic factors (61,62). However, it seems unlikely that genetic changes in the American population could be the cause of the dramatic increases in obesity over the past two decades. Furthermore, obesity is increasing in countries with a very small immigrant population and a presumably stable genetic base. In the Republic of Korea, the prevalence of obesity among school children in Seoul increased 4.6 times in males and 3.2 times in females from 1979 to 1996 (63). There is much speculation concerning the etiology of obesity, but no one factor can explain the cross-cultural, multinational increases in obesity. Easy access to good-tasting, high-fat foods and decreased physical activity has been suggested by some as the reason for increased incidence of obesity (64-66), but the evidence presented here suggests that the fat content of diets is not responsible for the occurrence of obesity. Humans appear to have the capacity to adapt to large differences in macronutrient composition in the diet. When 12 subjects were subjected to an abrupt change from a low fat diet to a high fat diet, all were able to adjust fat oxidation to match fat intake within 7 days, with no changes in body weight or energy expenditure (67). Indigenous populations exhibit extremely disparate composition in their traditional diets, without apparent ill effects at either extreme. A tropical diet is typically very low in fat and high in fiber and normally associated with lower incidence of obesity (though some have attributed that effect to temperature and not diet) (68,69). Even when obesity occurs in rural tropical populations there is evidence that is less associated with hypercholesterolemia, hypertriglyceridemia, and hyperglycemia (70). On the other hand, Eskimo populations have traditionally eaten very high fat diets but have lower incidence of obesity related disease than does the general population of the USA (71,72). These studies suggest that humans have the ability to adapt to large variations in macronutrient content of their diets, without adverse effects, provided there is ample, but not excessive energy intake and adequate intake of micronutrients.

We propose that the occurrence of obesity may be related to industrialization, prosperity and accompanying lifestyles. A recent descriptive study of individuals who were successful at long-term weight loss reported that 92% used exercise as a part of their weight-loss and weight maintenance program (73). A substantial body of evidence in humans and animals suggests that obesity is related to inactivity and activities associated with a lack of physical exercise, such as watching television (74-79). Storage of energy as body fat may be viewed as a mechanism for maintaining energy reserves when food is plentiful to facilitate survival during famine. However, what happens if there is no famine and food is always plentiful, easily obtained, and relatively inexpensive. This may be the dilemma much of the world is currently facing. Elimination of starvation in many areas of the world is certainly a positive development, however, when obesity related diseases such as diabetes and cardiovascular disease accompany prosperity in recently developed countries such as Korea (80,81), much of the benefit is negated. More study is needed to identify the causes of obesity and particularly the impact of an easily accessible and relatively inexpensive food supply on human obesity and health.

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