The effect of proportion of fat in hypo energetic diet on weight reduction and metabolic profile.

By

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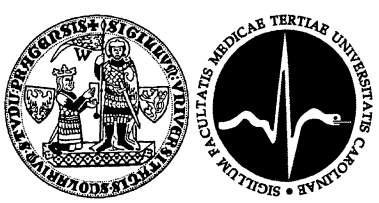

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Obesity

Obesity implies an excess storage of fat, and this can most easily be detected by looking at the undressed patient. Most patients suffer from simple obesity, but certain conditions have obesity as an associated feature, such as hypothyroidism and Cushing's syndrome.

The rapid spread of urbanization and industrialization and the dramatic lifestyle changes that accompany these trends have led to a pandemic of obesity, even in developing countries. The World Health Organization has predicted that, by 2020, two-thirds of the global diseases will be attributable to chronic diseases associated with obesity.

The increasing industrialization of agriculture has resulted in more processed foods, which in turn, has led to an increase in energy-dense foods that are high in carbohydrates and fat. Although there is some debate about the relative contributions of fat and carbohydrate in the diet to the increase in obesity, there is a general consensus that dietary changes are needed to both treat obesity and reduce the risk factors for obesity. How to achieve these goals is also subject to much discussion.

Recently, more research has focused on the balance between carbohydrate and fat as energy sources in the etiology and treatment of obesity. Such research will help answer the growing debate over the potential benefits and risks of restricting carbohydrate or fat as energy sources in the battle to reduce obesity.

The level of energy storage, or fatness, at which the risk of morbidity increases is set at a level agreed upon by researchers. The body-mass index (the weight in kilograms divided by the square of the height in meters) is easy to calculate and is sufficiently correlated with direct measures of body fatness (e.g., as measured by hydro densitometry) to be useful in defining obesity clinically. A body-mass index greater than 28 is associated with a risk of morbidity, such as stroke, ischemic heart disease, or diabetes mellitus, which is three to four times the risk in the general population. A central distribution of body fat (ratio of waist circumference to hip circumference, >0.90 in women and >1.0 in men) is associated with a higher risk of morbidity and mortality than a more peripheral distribution of body fat (waist: hip ratio, <0.75 in women and <0.85 in men) and may be a better indicator of the risk of morbidity than absolute fat mass.

The pathogenesis of obesity

The primary form in which potential chemical energy is stored in the body is fat (triglyceride). The high caloric density and hydrophobic nature of triglyceride permit efficient energy storage. The amount of triglyceride in adipose tissue is the cumulative sum over time of the differences between energy (food) intake and energy expenditure (mainly resting metabolism and physical activity). Although homeostatic mechanisms

keep this difference very close to zero (see below), very small imbalances over a long period can have a large cumulative effect. The current availability of calorically dense foods and an unhealthy lifestyle promote weight gain. For example, non obese adults ingest about 900,000 kcal of food per year. About 3500 kcal of chemical energy is contained in 0.45 kg (1 lb) of adipose tissue. If intake exceeded expenditure by 2 percent daily for a year, the result would be an increase of 18,000 kcal, or approximately 2.3 kg (5 lb). Because energy expenditure increases as weight increases, the weight gained would somewhat compensate for this imbalance. However, the 9.1 kg (20 lb) of weight gained by the average American man or woman between the ages of 25 and 55 years represents a remarkably small net imbalance between energy intake and expenditure — an excess intake of about 0.3 percent of ingested calories. This degree of control is achieved by coordinate effects on energy intake and expenditure mediated through endocrine and neural signals that come from adipose tissue and the endocrine, neurological, and gastrointestinal systems and are integrated by the central nervous system. Short-term (daily) food intake is not closely correlated with energy expenditure or energy stores in adults or children. One or more mechanisms are needed to integrate short-term determinants of energy intake (e.g., hepatic glycogen content, fatty-acid oxidation, and plasma glucose) with more direct monitoring of long-term energy stores (fat mass). Such integration is central to the regulation of body fat stores (Figure 1 and Figure 2).

The relative constancy of energy storage is the result of the coordinate activity of a complex system with components ranging from the highest cortical centers of the brain to the adipocytes; no single node or loop in the system functions in isolation. As shown in Figure 2, a large number of factors originating throughout the body send afferent signals to a smaller number of functional centers in the central nervous system, which then mediate interactions with efferent pathways to regulate energy expenditure (e.g., through the sympathetic and parasympathetic nervous systems and thyroid hormones) and energy intake (through eating behavior).

The substances shown in Figure 2 interact at many levels. The size of and interactions within this system make it unlikely that pharmacologic or surgical manipulation of a single component will lead to long-term resolution of obesity.

Numerous biopsychological factors impinge on eating behavior. The arcuate and paraventricular nuclei in the ventromedial hypothalamus are parts of a system integrating body composition with energy intake and expenditure. Afferent neural (vagal and catecholaminergic) stimuli and hormonal stimuli (e.g., insulin, cholecystokinin, leptin, and glucocorticoids) related to metabolic status are received in the hypothalamus, where they modulate the release of peptides known to affect food intake and efferent signals to the hypothalamic–pituitary axis (resulting in endocrine mediation of fuel disposition) and the autonomic nervous system (resulting in energy expenditure and insulin release). Although there has been considerable interest in dietary composition and weight fluctuations as determinants of body composition, these factors do not have major roles in the pathogenesis of obesity. Both protein and carbohydrate can be metabolically converted to fat, and there is no evidence that changing the relative proportions of protein, carbohydrate, and fat in the diet without reducing caloric intake will promote

weight loss. However, fat has a higher caloric density than protein and carbohydrate, and its contribution to the palatability of foods promotes the ingestion of calories.

The responses of both lean and obese humans to experimental manipulation of body weight support the hypothesis that body fat content is regulated; making it unlikely that behavior can be the sole determinant of obesity. The 24-hour energy expenditure per unit of lean body mass is similar in lean and obese subjects at their usual body weight. Small (10 percent) decreases in body weight result in declines in energy expenditure that persist despite a caloric intake that is sufficiently reduced to maintain the lower weight. Thus, a formerly obese person requires approximately 15 percent fewer calories to maintain a "normal" body weight than a person of the same body composition who has never been obese. This decline in 24-hour energy expenditure reflects approximately an 18 percent decrease in resting energy expenditure (resting cardio respiratory work, maintenance of transmembrane ion gradients, and so forth) and approximately a 25 percent decrease in nonresting energy expenditure (energy expended in physical activity), suggesting that the reductions in energy expenditure may be due in part to changes in the efficiency with which skeletal muscle converts chemical energy to mechanical work. These reductions in energy expenditure persist in adults who have maintained a reduced body weight for three to five years. Lean and obese subjects have equivalent increases in energy expenditure during the maintenance of an increased body weight.

In both obese and lean subjects who lose weight, there is an almost inevitable tendency, to regain the lost weight. The regained weight is probably due to physiologic factors that act to maintain the usual body weight, even when it is high.

In animals, some regulation of energy balance is achieved through metabolic cycles that consume ATP without performing useful biochemical work (futile cycles) — for example, simultaneous lipolysis and glyceride synthesis in fat cells and glycolysis and gluconeogenesis in the liver. Although small changes in energy expenditure through these cycles could theoretically affect body weight over time, there is little evidence that the cycles are important in energy homeostasis in humans. Substrate oxidation uncoupled from ATP generation in brown adipose tissue has also been hypothesized to be a mechanism for regulating body energy stores. Although brown adipose tissue is present in neonates, the extent to which it persists into adulthood and whether its amount or function in obese or formerly obese persons differs from that in persons who have never been obese are controversial. A protein (uncoupling protein 2) has recently been identified that uncouples substrate oxidation from the generation of ATP in white adipose tissue and muscle and that is up-regulated in mice fed high levels of fat. These findings suggest but do not prove that uncoupled mitochondrial respiration may act as an energy buffer in humans.

Mediators of energy homeostasis

Insulin

Plasma insulin concentrations are proportional to the adipocyte volume. Insulin gains access to the central nervous system through a saturable transport system and reduces food intake by inhibiting the expression of neuropeptide Y, enhancing the anorectic effects of cholecystokinin and inhibiting neuronal norepinephrine reuptake.

Cholecystokinin

Cholecystokinin, a peptide secreted from the duodenum in the presence of food, reduces food intake. There are two types of cholecystokinin receptors: type A predominates in the gastrointestinal system and type B predominates in the brain, especially in the nucleus of the tractus solitarius and area postrema. Only type A receptors bind the bioactive C-terminal octapeptide of cholecystokinin. The anorectic effect of cholecystokinin is blocked by abdominal vagotomy, suggesting that the primary site of action of cholecystokinin is in the periphery. Cholecystokinin does not cross the blood–brain barrier.

Other Endocrine and Peptide Signals

Numerous other hormones modulate fat storage through their effects on energy intake (e.g., glucocorticoids and glucagon), energy expenditure (e.g., androgens and thyroid and growth hormones), or the partitioning of stored energy between lean tissue and fat. In addition, in some genetically obese animals or those with obesity due to experimentally induced lesions in the ventromedial hypothalamus, adrenalectomy ameliorates the obesity, suggesting that treatment with glucocorticoid antagonists may be effective in some cases of obesity in humans. Other gut peptides, including gastrin-releasing peptide, neuromedin B, enterostatin, and amylin, may also contribute to the regulation of energy balance in humans.

Leptin

Leptin, encoded by the *Lep* gene, is synthesized in and secreted from adipose tissue and is a potential afferent signal of fat stores. In humans this gene is referred to as *LEP*. Systemic or intracerebroventricular administration of leptin reduces food intake and increases energy expenditure, resulting in reduced body fat and restoration of insulin-sensitive glucose disposal in *ob/ob* (leptin-deficient) mice. Very high doses of leptin have similar effects in non obese animals. Administration of leptin in rats deprived of food corrects many of the neuroendocrine changes (e.g., the decrease in the release of thyroid hormone) that occur as a result of food deprivation but does not alter the rate of weight loss. By virtue of its effects on growth hormone–releasing and gonadotropin-releasing hormones, the leptin-mediated signal may provide a critical link between somatic energy stores, on the one hand, and growth and fertility, on the other. The characteristics of this system are consistent with the concept of a lipostatic set point for weight regulation.

The expression of leptin in adipose tissue is increased by insulin, glucocorticoids, and estrogens and is decreased by β-adrenergic agonists and possibly by androgens. Leptin probably contributes to energy homeostasis in part by decreasing neuropeptide Y mRNA or blocking its action as an appetite stimulant

Although leptin exerts potent antiobesity effects in leptin-deficient rodents, its role in the pathogenesis or treatment of obesity in humans is unclear. Tentative linkage of some measures of adiposity to the region of the *LEP* gene has been reported in some groups of extremely obese whites and in a Hispanic population but not in the Pima Indians, in whom obesity and diabetes are extremely common. However, most obese persons do not have any abnormalities in the coding sequence for leptin.

Plasma leptin concentrations are increased in obese humans in direct proportion to body fat mass. Within a given fat depot, the expression of leptin mRNA is proportional to adipocyte volume, and rates of leptin production per unit of fat mass and of leptin clearance from the circulation are similar in obese subjects and those who have never been obese. Unlike *ob/ob* mice, in which the administration of leptin normalizes insulin-mediated glucose disposal, obese subjects with high plasma leptin concentrations have a resistance to insulin, and leptin diminishes the sensitivity to insulin in human cells in vitro.

In the aggregate, these findings suggest that the primary role of leptin may be to indicate whether somatic fat stores are sufficient for growth and reproduction. If the stores are inadequate — as reflected by a decline in plasma leptin concentrations to a level below a threshold that may be genetically and developmentally set — the result is hyperphagia, low energy output, and infertility. Plasma leptin concentrations above this threshold may have a minimal physiologic effect or none. Hence, obese humans with high plasma leptin concentrations have neither hypophagia nor hypermetabolism.

Leptin Receptors

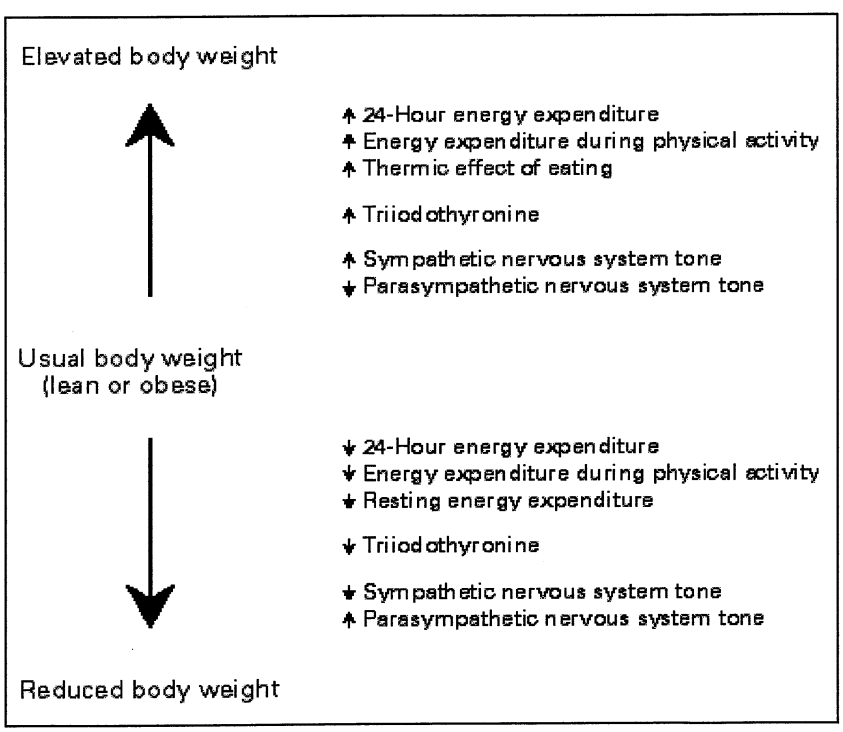
If leptin is a major afferent signal to the central nervous system regarding fat mass, human obesity may be the result of mutations or allelic variations in the leptin receptor, exemplified in diabetic (*db/db*) mice and Zucker fatty (*fa/fa*) rats. The leptin receptor is widely expressed (in the brain, lungs, kidneys, muscle, and adipose tissue). Distinct forms of the receptor apparently serve to transport leptin in the circulation and across cell membranes, and one isoform couples ligand binding to intracellular signaling of the action of leptin. If obesity in humans were due to a mutation affecting the ability of the leptin receptor to couple to its effector molecules, then obese persons might be expected to have higher plasma leptin concentrations than predicted on the basis of their fat mass, but this is not the case.

Neuropeptide Y

Neuropeptide Y links afferents reflecting the nutritional status of the organism from the endocrine, gastrointestinal, and central and peripheral nervous systems to effectors of energy intake and expenditure. The peptide is synthesized by cell bodies in the arcuate nucleus of the hypothalamus and transported axonally to the paraventricular nucleus, where the highest concentrations are found. (Neuropeptide Y is also synthesized and released from the adrenal gland and sympathetic nerves, but it does not cross the blood–brain barrier.)

Neuropeptide Y is a potent central appetite stimulant. The expression of neuropeptide Y mRNA is increased by insulin and glucocorticoids and decreased by leptin and estrogen. In rodents, food deprivation is associated with an increase in hypothalamic production of neuropeptide Y mRNA. The injection of neuropeptide Y into the paraventricular nucleus in rats stimulates food intake and increases lipoprotein lipase activity in white adipose tissue while decreasing sympathetic nervous system activity and thermo genesis in brown adipose tissue. Thus, centrally administered neuropeptide Y produces coordinate effects on energy intake and output that favor weight gain. Despite evidence of the physiologic importance of neuropeptide Y in energy homeostasis, neuropeptide Y–knockout mice have normal body fat and food intake, with normal hyperphagia when food is withheld. These findings highlight the extraordinary redundancy of systems regulating caloric storage.

Figure 1: Metabolic changes after weight gain or loss in adults.



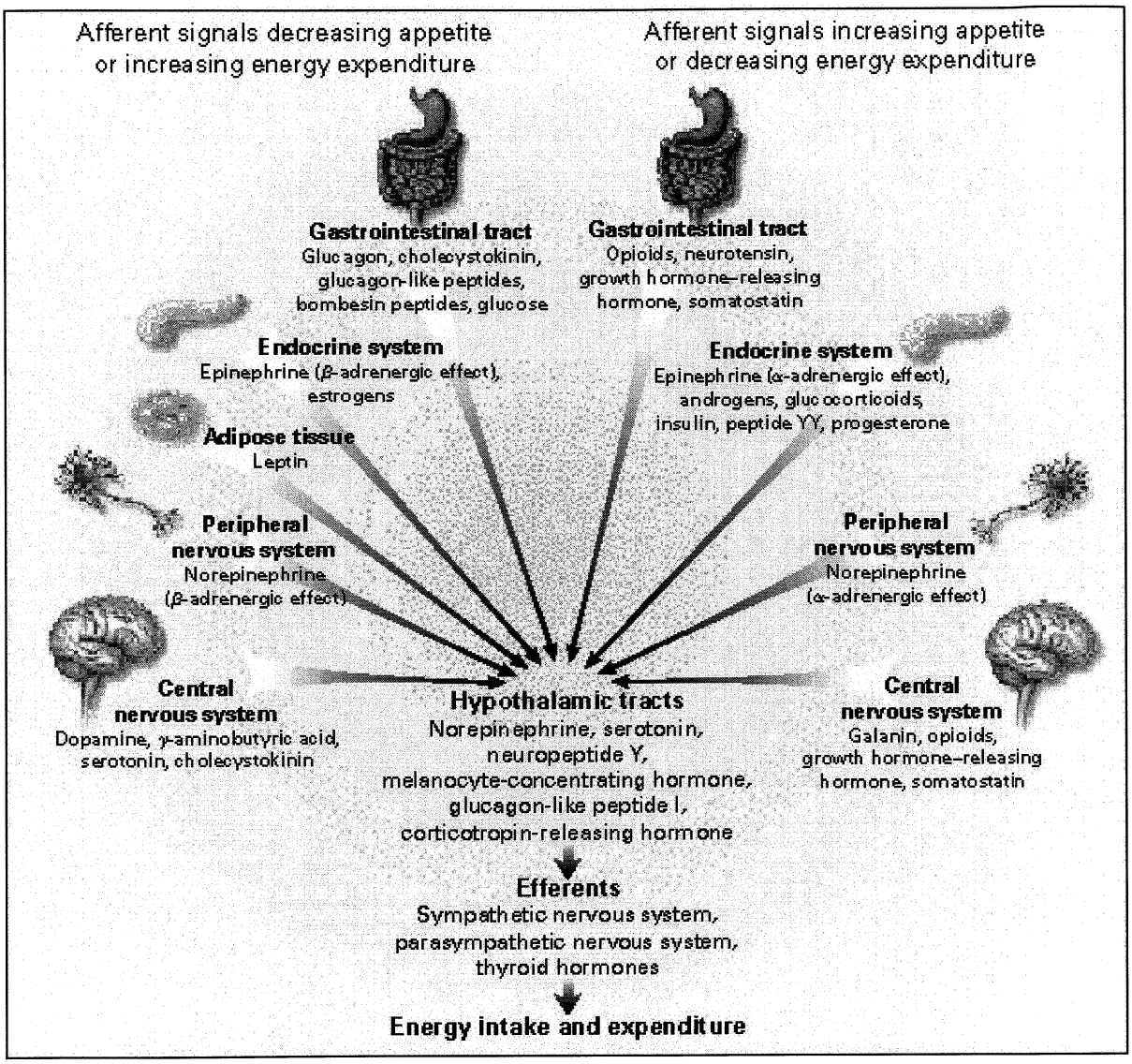


Figure 2. Molecules That Affect Energy Intake and Expenditure.

Treatment

The aim of weight reduction should be to decrease morbidity rather than to meet a cosmetic standard of thinness, and obese persons should be encouraged to set reasonable short-term goals for weight loss, bearing this aim in mind. They must recognize that any lifestyle alterations, in the form of increased exercise or decreased caloric intake, made to lose weight will need to be continued for life if the lower body weight is to be maintained. In general, maintaining a reduced weight through exercise and a diet that does not require medical supervision, without resorting to surgery or drugs, is more likely to be successful

in persons with mild obesity than in those with severe obesity. Despite the widespread use of various pharmacologic and surgical therapies since the 1950s, the prevalence of obesity continues to increase, and the results of treatment remain unsatisfactory. Approximately two thirds of persons who lose weight will regain it within one year, and almost all persons who lose weight will regain it within five years.

Diet

The composition of the ideal or most healthful diet is not known. However, weight-reducing diets that consist of drastically altered proportions of nutrients may be dangerous and no more effective than diets that contain at least minimal amounts of protein, essential fatty acids, vitamins, and minerals, according to age-specific recommendations, and are low in saturated fat. Given our current knowledge of the effects of diet on morbidity, it is logical to assume that such a diet, especially if combined with regular exercise, will diminish the severity of cardiovascular risk factors (e.g., hyperlipidemia), even though it may not affect body composition. There is some evidence that low-fat diets may enhance short-term weight loss and, if continued, help maintain the reduced body weight.

Exercise

Increased physical activity not only increases caloric expenditure but also promotes dietary compliance. Exercise may increase the desire for foods that are high in carbohydrates and reduce the desire for foods that are high in fat. Thus, treatment programs for obesity that include physical activity may be more successful than those that do not. Different types of exercise may affect fuel use differently. Intermittent exercise (high intensity followed by low intensity) results in a greater reduction in weight and fat than continuous exercise of low-to-medium intensity that involves expending the same number of calories.

Behavioral therapy

Although psychological disturbances are not often the primary cause of obesity, behavior modification based on an analysis of the circumstances in which a person tends to eat and the particular meaning of eating for that person can be helpful for weight reduction. Experts in this approach recommend that persons receive advice or counseling in a stable group setting for a long period and that close contact with the therapist and members of the group be maintained after weight has been lost.

Drug Therapy

The amphetamine-like actions of sympathomimetic drugs (phentermine, phenmetrazine, phendimetrazine, diethylpropion, mazindol, and phenylpropanolamine) that increase brain concentrations of catecholamines or act directly on catecholamine receptors to increase the activity of β-adrenergic systems (resulting in decreased appetite or increased energy expenditure) or decrease the activity of α-adrenergic systems (resulting in increased appetite or decreased energy expenditure) make the drugs unsuitable for obese persons with evidence of cardiovascular disease. Serotonin-reuptake inhibitors have recently been favored as appetite suppressants. One of the newer of these agents, fenfluramine, was approved for use by the Food and Drug Administration (FDA) in 1996. The serotonergic drugs do not raise blood pressure or increase the metabolic rate and are usually well tolerated. The combination of phentermine and fenfluramine has found favor on the basis of a four-year study of 121 subjects; the average weight loss was 11 kg (24 lb) at two years and 9.4 kg (21 lb) at three years (with no sustained weight loss in the control group), although fewer than half the subjects completed the study. Whenever the drugs were stopped, weight was promptly regained. Fluoxetine and other selective serotonin-reuptake inhibitors used for the treatment of depression promote some weight loss for at least five to six months.

Serotonin-reuptake inhibitors may increase the likelihood of primary pulmonary hypertension, although it has been argued that for obese persons, the benefit of weight reduction with the use of these drugs outweighs the risk associated with their use. However, observations by Connolly et al. suggest that valvular heart disease may be associated with the use of fenfluramine and phentermine.

Sibutramine, a drug with both catecholaminergic and serotonergic agonist effects. Other drugs under development include β_3-adrenergic–receptor agonists and other chemicals that act to increase caloric expenditure (e.g., BRL 26380A and ephedrine) and a lipase inhibitor (tetrahydrolipstatin) that prevents the digestion and absorption of ingested fats. No currently available therapy addresses the central mechanisms regulating body weight. Although the administration of leptin causes weight loss in some leptin-deficient rodents, most obese persons do not have a deficiency of this protein. Since plasma leptin concentrations fall during hypocaloric intake, the administration of leptin might prove useful in promoting adherence to dietary regimens and maintenance of reduced body weight.

Lipase inhibitors such as Orlistat are a peripherally acting inhibitor of pancreatic and gastric lipase. It reduces dietary fat absorption and aids weight loss. It often causes gastrointestinal side effects.

Any drug therapy should be administered with recommendations for dietary modifications and exercise.

Surgical Therapy

Surgery is usually recommended only for persons with severe obesity (body-mass index, >40) or those with less severe obesity (body-mass index, 35 to 40) who have coexisting conditions. Jejunoileal shunts lead to substantial weight reduction, and 10 years after surgery, approximately 80 percent of patients remain at least 10 percent below their preoperative body weight. This procedure, however, frequently results in symptoms related to the presence of a blind loop. The more commonly performed procedure is gastric reduction (gastroplasty) with or without an intestinal bypass. Gastroplasty with a bypass can initially result in substantial weight loss, and approximately 80 percent of patients remain at least 10 percent below their preoperative body weight for 10 years after surgery, although the success rate is substantially lower in patients with a craving for foods high in carbohydrates. The efficacy of the procedure is probably due to the increased sense of fullness with a reduced gastric volume and the symptoms of "dumping" associated with the passage of gastric contents into the intestines, which act as deterrents to eating. Excess consumption of liquid or semisolid foods can negate the benefits of surgery. Patients who undergo gastroplasty must be followed carefully for possible intestinal obstruction and electrolyte disturbances.

Focus on dietary therapy

In the majority of overweight and obese patients, adjustment of the diet to reduce caloric intake will be required. Dietary therapy consists, in large part, of instructing patients on how to modify their diets to achieve a decrease in caloric intake. A key element of the current recommendation is the use of a moderate reduction in caloric intake to achieve a slow but progressive weight loss. Ideally, caloric intake should be reduced only to the level required to maintain weight at the desired level. If this level of caloric intake is achieved, excess weight will gradually disappear. In practice, somewhat greater caloric deficits are used in the period of active weight loss, but diets with very low calories are to be avoided. Finally, the composition of the diet should be modified to minimize other cardiovascular risk factors.

The centerpiece of dietary therapy for weight loss in overweight patients is a low-calorie diet (LCD) (800 to 1,500 kcal/day). This diet is to be distinguished from a very low-calorie diet (VLCD) (250 to 800 kcal/day), which has been unsuccessful in achieving weight loss over the long term. The LCD recommended in this report also contains a nutrient composition that will decrease other risk factors, notably, high serum cholesterol and hypertension.

Evidence Statement: *LCDs can reduce total body weight by an average of 8 percent and help reduce abdominal fat content over a period of approximately 6 months. Evidence Category A.*

Rationale: A decrease in caloric intake is the most important dietary component of weight loss and maintenance. LCDs have been shown to reduce total body weight by an average of 8 percent over a period of 6 months, accompanied by significant reductions in waist circumference. When weight loss occurs, the loss consists of about 75 percent fat and 25 percent lean tissue. A deficit of 500 to 1,000 kcal/day will produce a weight loss of 70 to 140 grams/day, or 490 to 980 grams/week (1 to 2 lb/week). A deficit of 300 to 500 kcal/day will produce a weight loss of 40 to 70 grams/day, or 280 to 490 grams/week (1/2 to 1 lb/week). A patient may choose a diet of 1,000 to 1,200 kcal for women and 1,200 to 1,500 kcal for men.

VLCDs (less than 800 kcal/day) are not recommended for weight loss therapy because the deficits are too great, and nutritional inadequacies will occur unless VLCDs are supplemented with vitamins and minerals. Moreover, clinical trials show that LCDs are just as effective as VLCDs in producing weight loss after 1 year.

Although more weight is initially lost with VLCDs, more is usually regained. Further, rapid weight reduction does not allow for gradual acquisition of changes in eating behavior. Successful behavior therapy is the key to long-term maintenance of weight at a reduced level. Finally, patients using VLCDs are at increased risk for developing gallstones.

Successful weight reduction by LCDs is more likely to occur when consideration is given to a patient's food preferences in tailoring a particular diet. Care should be taken to be sure that all of the recommended dietary allowances are met; this may require use of a dietary supplement. Dietary education is a necessary ingredient in achieving adjustment to an LCD. Educational efforts should pay particular attention to the following topics:

- Energy value of different foods;
- Food composition: fats, carbohydrates (including dietary fiber), and proteins;
- Reading nutrition labels to determine caloric content and food composition;
- New habits of purchasing: preference to low-calorie foods;
- Food preparation: avoiding adding high-calorie ingredients during cooking (e.g., fats and oils);
- Avoiding over consumption of high-calorie foods (both high-fat and high-carbohydrate foods);
- Maintaining adequate water intake;
- Reducing portion sizes;
- Limiting alcohol consumption.

Rationale: Many studies suggest that the rate of weight loss diminishes after about 6 months. Shorter periods of dietary therapy usually result in lesser weight reductions. Therapeutic efforts should be directed toward behavior therapy as well as maintaining LCDs.

Evidence Statement: *During dietary therapy, frequent contacts between professional counselors and patients promote weight loss and maintenance. Evidence Category C.*

Rationale: Frequent clinical encounters during the initial 6 months of weight reduction appear to facilitate reaching the goals of therapy. During the period of active weight loss, regular visits of at least once per month and preferably more often with a health professional for the purposes of reinforcement, encouragement, and monitoring will facilitate weight reduction. Weekly group meetings can be conducted at a low cost, and can contribute to favorable behavior changes. However, no clinical trials have been specifically designed to test the relative efficacy of different frequencies of encounters with physicians, dietitians, or others on the weight loss team.

Evidence Statement: *The amount of time spent with the patient favorably affects weight change in overweight or obese adults given dietary therapy. Evidence Category D.*

Rationale: Training of health professionals in techniques of weight reduction, especially in behavior therapy and dietary principles, is expected to facilitate weight reduction. Further, adequate time must be made available to the patient to convey the information necessary, to reinforce behavioral and dietary messages, and to monitor the patient's response.

Evidence Categories

Evidence Category	***Sources of Evidence***	***Definition***
A	Randomized controlled trials (rich body of data)	Evidence is from endpoints of well-designed RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A therefore requires substantial numbers of

		studies involving substantial numbers of participants.
B	Randomized controlled trials (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
C	Nonrandomized trials Observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel Consensus Judgment	Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C).

Effect of proportion of fat in a hypo energetic diet.

As mentioned earlier, to achieve success in loosing weight, one needs to get an negative energy balance. There is a big debate regarding the optimal macronutrient composition, and before it is possible to give a good answer it is important to have a better evidence based fundament. Some trials demonstrate that ad libitum low fat diets produce 3-4kg weight loss over 3-6 months, and some evidence implies that weight maintenance is easier to achieve with a fat reduced diet than with a higher fat diet(7). There is little evidence supporting any big difference between low fat diets with complex and simple carbohydrates, higher protein content might improve weight loss (9, 12).

Very few randomized trials have been conducted, which combine energy restriction, and compare different levels of energy from fat and carbohydrate. Most studies done have included only small groups of obese subjects, and so have less statistical power.

Dietary composition affects risk factors of cardiovascular disease and type 2 diabetes independently of weight loss. By increasing total energy from carbohydrates while decreasing percentage of energy from fat may lower fasting plasma total and low-density lipoprotein-cholesterol and also high-density lipoprotein cholesterol concentrations, and increase, at least initially fasting plasma triacylglycerol concentration (11). These same changes in diet lead to lowering of fasting plasma insulin concentrations. This reflects the increase in whole body insulin sensitivity. However it is less clear which diet is the most beneficial during hypo energetic dieting.

In a randomized study done by M Petersen et al, they used a low fat diet composed of 20-25% of total energy from fat, 15% protein, and 60-65% carbohydrates for one group, and a high fat diet composed of 40-45% total energy from fat, 15% protein, and 40-45% from carbohydrates for the other. Both of these diets were hypo energetic. The whole study lasted for 10 weeks. 648 subjects completed the trial.

There was an average of 6.9kg reduction of body weight in the low fat group and 6.6kg in the high-fat group. Of the people completing the trial, more subjects lost >10% in the low fat group, than in the high fat group. There was a decrease in fasting plasma total, low density lipoprotein and high density lipoprotein –cholesterol in both groups, but more pronounced in the low fat group. Fasting plasma insulin and glucose were lowered equally by both diets. There were fewer dropouts in the low fat diet.

Fat content in diet

In a meta-analysis study done by A Astrup et al, they went over ad libitum dietary intervention studies done from 1966 to 1999, to try to evaluate the efficacy of low fat diets in reducing body weight. The low fat diet without restrictions in energy intake clearly showed to cause more weight loss (3.2 kg in average), than control groups consuming a habitual diet or a medium-fat diet ad libitum. The low fat diet also led to decreased energy intake. 16 trials were evaluated, with duration of 2-19 months, enrolling 1910 individuals. However, none of the studies included in this analysis had group of subjects with BMI >30. (8)

The study done by R James Stubbs et al, where they fed a low, medium and high fat diet to a group of seven men ad libitum, they concluded that high fat diet produce a higher ad libitum energy intake than do low fat diets.(10) This incorporates well into a large group of short term studies done, showing that fat is less satiating than carbohydrate and protein when compared joule to joule, and that high-fat foods are more likely than low fat foods to induce passive over consumption and weight gain.

In the study done by PH Bisschop et al, where they compared the different amounts of fat in diet and its effect on hepatic and peripheral insulin sensitivity. Six healthy men were studied on 3 occasions after consuming for 11 d diets with identical energy and protein contents but different percentages of energy as fat and carbohydrate as follows: 0% and 85% [low-fat, high-carbohydrate (LFHC) diet], 41% and 44% [intermediate-fat, intermediate-carbohydrate (IFIC) diet], and 83% and 2% [high-fat, low-carbohydrate (HFLC) diet]. They concluded that a high-fat, low-carbohydrate intake reduces the ability of insulin to suppress endogenous glucose production and alters the relation between oxidative and nonoxidative glucose disposal in a way that favors storage of glucose.

Experimental study

Objective: To investigate if a hypo-energetic low-fat diet is superior to a hypo-energetic high-fat diet for the treatment of obesity, inducing weight-loss and producing a positive effect on metabolic profile.
Design: Open-label, 10 week dietary intervention comparing two hypo-energetic (-600kcal/day) diets with a fat energy percent of 20-25 or 40-45.
Subjects: Obese (BMI $\geq$ 30kg/m^2) adult subjects (n = 44), from Czech Republic.
Measurements: Body weight loss, blood lipid profile, insulin and glucose.

Subjects and methods

Protocol

The study was part of a randomized, parallel, two-arm, open-label 10-week dietary intervention of two hypo energetic diets, taking place in eight sites in seven European countries. The trial was part of a study of gene-nutrient interactions in physiology and dietary treatment of obesity.

Subjects

The study included 44 Caucasian Europeans (34 women). Mean bodyweight was 105kg. Inclusion criteria were BMI $\geq$30kg/m^2 and age 20-50. Exclusion criteria were weight change >3kg within 3 months before the start of the study, hypertension, diabetes or hyperlipidemia treated by drugs, untreated thyroid disease, surgically or drug-treated obesity, pregnancy, participation in other trials, alcohol or drug abuse. Participants were recruited through the media, from waiting lists, ongoing population studies, by self-referral or referral from a general physician or other clinical units and local obesity organizations.

Diets

The main macronutrient of the two diets was: low-fat diet – 20-25% of total energy from fat, 15% from protein and 60-65% from carbohydrate; high-fat diet – 40-45% of total energy from fat, 15% from protein and 40-45% from carbohydrate. Both diets were designed to provide 600kcal/day (1 kcal= 4.2 kJ) less than the individually estimated energy requirement based on an initial resting metabolic rate multiplied by1.3. Subjects were given oral and written instructions relating to these targets based on either a template or an exchange system. Instructions were also given to minimize differences between the two diets in other components such as sources and types of fat, amount and type of fiber, type of carbohydrate, fruit and vegetables, and meal frequency. Subjects were requested to abstain from alcohol consumption. Dietary advice reflected local customs, and all food items were purchased by the subjects themselves. The dietary instructions were reinforced weekly. At each session, the dietician and the participant rated compliance equal to 1.

A 3-day-weighed food record of two weekdays and one weekend day was performed before the study and during the last week of the intervention. One-day-weighed food records were completed in the 2nd, 5th and 7th weeks. The dietary records were analyzed using the food-nutrient database routinely used in each center.

Statistical analysis

The tests were made using GLM (ANOVA) for repeated measure. The results were compared using Wilcoxon. P-values in tables are from GLM. The statistical software SPSS version 11.5 was used. Statistical significance was set at $P<0.05$.

Results

	High-fat diet		Low-fat diet		
Variable	Baseline (s.d)	Decrease (s.d)	Baseline (s.d)	Decrease (s.d)	Difference in mean change(P-value)
Weight(kg)	104,76 (18,54)	7,14 (3,67)	105,24(17,8)	7,6(2,9)	-0,46 (not significant)
Waist circumference(cm)	105,2 (13,31)	4(5,78)	106,5(11,3)	7(3,84)	-3 (not significant)
Waist hip ratio	0,87 (0,094)	0(0,05)	0,87(0,13)	0,01 (0,06)	-0,01 (not significant)
HDL-cholesterol(mmol/l)	1,19(0,4)	0,02 (0,19)	1,16 (0,28)	0,08 (0,21)	-0,06 (not significant)
VLDL(mmol/l)	0,47(0,36)	0,12 (0,23)	0,35 (0,12)	0,02 (0,14)	0,1 (0,118)
Triacylglycerol(mmol/l)	1492 (1172)	323,1 (591,7)	1156 (564)	-70 (414,9)	393,1 (0,012)
Insulin(µmol/l)	12,9(10,3)	1,62(9,72)	10,1(4,75)	2,28(7,3)	-0,66 (not significant)
LDL-cholesterol(mmol/l)	3,4(1)	0,12 (0,41)	3,49 (0,75)	0,41 (0,52)	-0,29 (0,044)

Body weight and composition.

Mean weight loss in the low-fat diet was 7, 4 kg, compared to 7, 6 kg on the high-fat diet. There was a decrease in waist circumference and waist-hip ratio, but none of these findings had statistical significance between the groups.

Plasma lipids and insulin.

There was a decrease in all variables, for both diets except for plasma triacylglycerol, which increased on the low fat diet (see table). There was a statistically significant decrease in Triacylglycerols using a high fat diet, compared to the low fat diet.

There is also a statistically significant decrease in LDL-cholesterol in the low fat group compared to the high fat group.

Discussion

This 10-week randomized trial of two hypo-energetic diets with either low- or high-fat content, involving 44 obese subjects, demonstrates that the two diets were not very different in producing a clinically significant weight loss in both women and men. The LDL-cholesterol was lowered more in the low fat group, and triacylglycerol was lowered more in the high-fat group. These findings go well with the findings in the larger study by M Petersen et al, that the two diets are not very different in producing a clinically significant weight loss(2). The findings on the lipid profile could be explained by the low number of subjects investigated.

Some studies using a short-term test meal studies with calorie for calorie comparison suggests that carbohydrate is more satiating than fat and that overeating may be more likely with a high fat diet because of the higher energy density and greater sensory pleasure (10). The present study demonstrates that these potential differences produced by energy-fixed diets with various fat and carbohydrate contents do not translate into overall weight loss differences. It is never the less important to stress that this trial only lasted for 10 weeks, and this is a relatively short time in a weight managing program, and diet compliance and tolerability might have more important influence on weight loss outcomes in long-term studies.

The slight reduction observed in HDL-cholesterol is very likely owing to negative energy balance at the time of measurement. The effect on diet per se on HDL-cholesterol cannot be seen before the subjects are weight stable. In previous studies, the undesirable reduction in HDL-cholesterol brought about by a low-fat diet had returned to baseline concentration by 6 months (14). The decrease in blood lipids is primarily a result of weight loss per se. This study additionally demonstrates that both diets have beneficial effects on blood lipids.

The increase in Triacylglycerol observed in the low fat diet group, could be explained by the increased hepatic fatty acid availability, resulting from reduced hepatic fatty acid oxidation (15).

Conclusion

This study shows that when considering the effects of a hypo energetic high-fat diet vs. low fat diet, both produce beneficial effects on weight loss. There were beneficial effects on lipid profile with both diets, however the high-fat diet the Triacylglycerol levels were significantly lowered compared to the low-fat diet. LDL-cholesterol was lowered significantly more by the low-fat diet.

References

1. Wylie-Rosett J. Paradigm Shifts in Obesity Research and Treatment: Introduction. Obesity Research 2004; 12: 85-87.

2. Petersen M, Taylor MA, Saris WHM, Verdich C, Toubro S, Macdonald I, Rössner S, Stich V, Guy-Grand B, Langin D, Martinez AJ, Pedersen O, Holst C, Sørensen TIA, Astrup A and the NUGENBOG Consortium. Randomized, multi-center trial of two hypo-energetic diets in obese subjects: high- versus low-fat content. International Journal of obesity 2006;

3. Rosenbaum M, Liebel RL, Hirsch J. Obesity. N Engl J Med 1997; 337: 396-407

4. Bonow RO, Eckel RH. Diet, Obesity, and Cardiovascular Risk. N Engl J Med 2003; 348: 2057-2058.

5. Bisschop PH, Metz J de, Ackermans MT, Endert E, Pijl H, Kuipers F, Meijer AJ, Sauerwein HP, Romijn JA. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. Am J Clin Nutr 2001; 71: 554-559.

6. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T,Williams M, Gracely EJ, Stern L. A Low Carbohydrate as compared to a Low fat diet in severe obesity. N Engl J Med 2003; 348: 2074-2081.

7. Toubro S, Astrup A. Randomised comparison of diets for maintaining obese subjects weight after major weight loss: ad lib, low fat, high carbohydrate diet *v* fixed energy intake. BMJ 1997; 314: 29-34.

8. Astrup A, Grunwald GK, Melanson EL, Saris WHM, Hill JO. The role of low fat diets in body weight control: a meta-analysis of ad libitum intervention studies. Int J Obes Relat Metab Disord 2000; 24: 1545-1552.

9. Saris WHM, Astrup A, Prentice AM, Zunft HJH, Formigura X, Verboeket- van de Venne WPHG et al. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. Int J Obes Relat Metab Disord 2000; 24: 1310-1318.

10. Stubbs RJ, Prentice AM, Ritz P, Coward WA.. Covert manipulation of the ratio of dietary fat to carbohydrate and energy density: effect on food intake and energy balance in free-living men eating ad libitum. Am J Clin Nutr 1995; 62: 330-337.

11. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb 1992; 12: 911-919.

12. Due A, Toubro S, Skov AR, Astrup A. Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomized 1-year trial. Int J Obes Relat Metab Disord 2004; 28: 1283-1290.

13. Freedman MR, King J, Kennedy E. Popular diets: a scientific review, Executive summary. Obesity Research 2001; 9: 1-5.

14. Golay A, Eigenheer C, Morel Y, Kujawski P, Lehmann T, de Tonnac N. Weightloss with low or high carbohydrate diet? Int J Obes Relat Metab Disord 1996; 20:1067-1072.

15. Mittendorfer B, Sidossis LS. Mechanism for the increase in plasma triacylglycerol concentrations after consumption of short-term, high-carbohydrate diets. Am J Clin Nutr 2001; 73: 892-899.