FAT REPLACERS AND FAT BLOCKERS

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INTRODUCTION

The motivating force behind fat substitutes is the consensus that excess of energy intake and high fat diets create health risks. Consumption of a diet rich in fat has been identified as a risk factor for excess energy intake, positive energy balance and the development of obesity (1,2). High fat diets, especially saturated fat, have been associated with atherosclerosis and cardiovascular disease. The onset of diabetes as well as the degree of glycemic control has been related to dietary fat intake. Lastly, a strong association exists between fat in the diet and certain types of cancer, for example, colon cancer.

Obesity poses a public health problem health problem with its growing incidence due to acculturation. Its treatment is often disappointing. Obesity treatment may include drugs that reduce food intake, drugs that increase energy expenditure and drugs that effect nutrient partitioning or metabolism. This disease requires concerted efforts and long-term treatment warranting all pharmacoagents to be considered carefully. Noradrenergic appetite suppressants (phentermine) result in weight loss, but their stimulatory effect limit their use. The serotonergic agents (fenfluramine, dexfenfluramine) are effective weight loss drugs, but were voluntarily withdrawn in USA because of cardiovascular and pulmonary complications. The combined noradrenergic-serotonergic agent, sibutramine is indicated in obesity, particularly in presence of cardiovascular risk factors. Weight loss is achieved with sibutramine, but weight gain is significant on discontinuation.

Newer antiobesity agents such as beta adrenoreceptor agonists (which increase thermogenesis), leptin and neuropeptide Y are currently under investigation. Most weight loss agents do result in initial weight loss, but sustained weight loss is not always achieved, even with continuation of treatment. The effect of weight loss obtained with pharmacological agents on morbidity and mortality have not been established. Considering these drawbacks of pharmacotherapy of obesity, dietary manipulation assumes great importance (3).

Dietary guidelines, in most countries encourage its population to reduce fat intake, as a proportion of calories from an average of 38% to 30% (4). However, dietary change is not easy because multiple biological and behavioral factors govern food intake. Physiological, cultural and cognitive factors interact and their effects on food choices and dietary patterns are poorly understood and somewhat unpredictable. Reversal of dietary patterns developed over decades is difficult to achieve. Thus, macronutrient substitutes in general and fat substitutes in particular have a logical role to play in achieving this dietary change without large changes in the dietary pattern.

TYPES OF FAT REPLACERS

Fat replacers are ingredients designed to replace all or part of the fat in a product, with minimum impact on the organoleptic quality of the food product. Fats provide many important attributes to foods like flavour, palatability, mouth feel and creaminess. Fat replacers are meant to serve these functions. They are of 3 types: fat mimetics, low caloric fats and fat substitutes (5).

FAT MIMETICS

Fat mimetics are materials belonging to other macronutrient categories i.e. carbohydrates or proteins, which replace the bulk, body and mouthfeel of fats. Examples include starch, cellulose, gums and dextrins among carbohydrates and whey, zein, microparticulated egg plus milk protein among proteins. These mimetics are digestible but less energy dense than fats, since they are carbohydrates or proteins. As these constituents are hydrated, the caloric reduction is even greater due to dilution. Fat mimetics are generally used in hydrated products like desserts and spreads. They are well understood biologically and of little risk when used at proposed levels. However they suffer from sizable sensory and functional limitations as general fat replacers. They cannot be used as a frying media and their high associated water content may reduce product shelf life(6).

LOW CALORIE FATS

The second category of low calorie fats includes triglycerides that are chemically altered to become less energy dense, i.e. to provide fewer than 9 Kcal/g. Examples are medium chain triglycerides

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(MCT), caprenin and salatrim. Medium chain triglycerides are triglycerides made up of 8-12 carbon fatty acids that provide 7 to 8 Kcal/g. Medium chain triglycerides are rapidly absorbed from the portal blood stream. They provide small caloric advantages but significant metabolic advantages. Caprenin is a triglyceride in which two fatty acids are medium chain fatty acids (caprylic and capric), and the third is behenic acid. Behenic acid is poorly absorbed. Thus caprenin provides 5 kcal/g rather than 9 kcal/g from normal fats and oils. Salatrim is a randomized triglyceride containing short and long chain fatty acids. The short chain fatty acids are acetic, propionic and butyric, while long chain fatty acids include stearic acid. The stearic acid and other long chain fatty acids are poorly absorbed. The caloric value of salatrim is about 5 kcal/g.

FAT SUBSTITUTES

Fat substitutes are materials that have the properties of fats and oils but are not absorbed or metabolised by the body. Examples include olestra, sorbestrin and esterified propoxylated glycerol esters (EPGs). Sucrose polyester or olestra developed by Procter and Gamble is a mixture of hexa, hepta and octa fatty acid esters of sucrose. The fatty acid distribution can range from 8 to 22 carbon fatty acids, saturated or unsaturated. The wide range of fatty acids allows the formation of various sucrose polyesters ranging from a liquid, to a plastic, to a hard fat. Olestra is not digested or absorbed by the human body. Thus its caloric value is close to zero. The other advantages are that it keeps its fat like qualities when heated and it carries flavours well. Since olestra cannot be digested, has a unique molecular structure and would be present in foods at levels comparable to the fat it was replacing, it had to be approved not only as a food additive but also as a macro ingredient. Hence a nutrition based review had to be done in addition to a toxicolology based review. Clinical testing indicated that olestra reduced the absorption of fat soluble vitamins and also caused abdominal cramping and loose stools in some individuals. Hence olestra products are fortified with fat soluble vitamins and a warning that abdominal cramping and loose stools may be produced is printed on the label. There are studies to show that using olestra improves the lipoproteins concentrations in hypercholesterolemic patients. Both 16 and 32 g/day doses of olestra were found to lower LDL cholesterol by 4-5% in subjects with moderately elevated cholesterol (7). In another study, LDL cholesterol was reduced by 16% and triglycerides by 20%, both of which were significantly different from the group treated with a low fat diet alone (8). The mechanism of action of olestra in lowering cholesterol is not only due to decreased saturated fat intake, but also due to reduced absorption and increased excretion of cholesterol. However, the lipid lowering associated with olestra may not be duplicated with other fat substitutes.

Sorbestrin, like olestra is indigestible. It is a hexa fatty acid ester of sorbitol and does not provide any calories. Arco Chemical Corporation has developed a family of non caloric fats that are esterified propoxylated glycerol esters (EPG). Esterified propoxylated glycerols are made from naturally occurring fats with propylene oxide inserted between glycerol and fatty acids. Any fat can be altered to produce its EPG counterpart. Thus a range of oils and fats can be manufactured. Like olestra, EPG's are not digested or absorbed by the gastro intestinal tract.

IMPACT OF FAT REPLACERS ON NUTRIENT AND ENERGY INTAKE

Obesity is the result of positive energy balance, an excess of energy intake over expenditure. Both genetic and environmental factors are responsible for obesity. It is likely that genes that affect energy intake as well as expenditure are involved. The role of leptin as a putative factor in signaling the extent of fat mass to the central nervous system and controlling both food intake and energy expenditure is unclear at this time.

Apart from the genetic factors mentioned above, the patho environment includes a high fat diet and lack of exercise. High fat diets have been shown to increase energy intake (9). This is probably due to the minimal appetite suppressant effect of fat, its high energy density, its high palatability and hedonic attributes of a high fat diet (10). Conversely, decreasing energy density by covertly removing dietary fat led to lower levels of energy intake (2). Thus early studies showed that decreasing the fat content of the diet by using fat replacers is usually attended by a modest decrease in energy intake and a significant weight loss (11). In other words, compensation for decreased energy intake does not occur or occurs only partially.

Unfortunately, most of this research was conducted on fairly small patient populations within the confines of a laboratory or clinic or on free living healthy subjects given fixed meals or

limited food selections and has generally been of short duration (1 to 14 days). More recent studies have demonstrated that unless a willful effort is made to reduce intakes or strictly control diet composition, consumers are likely to compensate for most or all of the energy reduction of fat substituted foods probably by increasing consumption of other macronutrients i.e. carbohydrates and proteins. (12,13,14). Hence, although weight loss may occur initially in these studies, a long term sustained reduction in energy intake and weight loss may be limited if the dietary strategy of fat replacement is used in isolation.

Although long term weight loss may be limited, these recent studies confirmed that use of fat replacers reduces fat intake and the percent of energy derived from fat. Thus although fat replacers may be a limited tool when used in isolation against obesity, the advantages accrued due to decreasing total and saturated fat remain i.e. in the prevention and treatment of cardiovascular disease, diabetes and certain forms of cancer. Also, use of reduced fat foods can play a valuable part in helping consumers achieve their dietary goals while still obtaining adequate intakes of vitamins and minerals (15).

FAT REPLACERS AND CONSUMER BEHAVIOR ISSUES

Certain issues still remain unresolved. The studies described above do not discount the possibility of cognitive behavioural responses, such as described by Caputo and Mattes (16), who found that subjects exhibited increases in self-selected fat intakes during periods in which they had been given what they believed to be lower fat meals. Concern has also been expressed that increased interest might be directed by consumers to certain foods (eg. those traditionally rich in fat) that they presently avoid on nutritional grounds, and consumption of these products might therefore increase at the expense of more nutrient dense items (17). Lastly there are consumer issues relating to the potential cost associated with use of fat substituted and reduced energy versions of foods. Future research should particularly focus on prospective dietary intervention trials conducted under extended realistic conditions to assess the actual patterns of nutrient and energy intakes that result from informed use in normal eating (18).

FAT REPLACERS: IMPLICATIONS OF USE

There are a number of advantages implicit in the use of fat substitutes. First by reducing the energy density of food, the nutrient-to-energy ratio of various foods is increased. Secondly, the fat content of the diet is reduced and the benefits of fat reduction on various chronic diseases is acheived. Thirdly, consumers are not required to make large changes in their habitual dietary patterns to achieve their dietary goals. However, consumption of fat substituted foods probably should not be relied on to produce spontaneous improvements in body weight management or obesity. Fat substituted foods could aid some individuals as part of an overall willful effort to control their diet. Changes in behaviour will continue to be a necessary adjunct to any technology-related changes in foods (5).

Although the use of fat substitutes is a potentially important strategy that, in general, poses little risk, there are still many unanswered questions. Hence cautious introduction of these products into the current food system and post marketing surveillance is essential.

FAT BLOCKERS

Orlistat (xenical) chemically known as tetrahydrolipstatin is a specific and potent inhibitor of gastric and pancreatic lipases. It is hydrophobic, amphipathic and water insoluble in nature. Orlistat is ideally situated in the surface layer of emulsion particle membranes for interaction with enzymes that superficially bind to such surfaces (19). It exerts its effect in the lumen of the stomach and small intestine. Orlistat acts by binding covalently to the serine residue of the active site of gastric and pancreatic lipases thus inactivating these enzymes. Hence systemic absorption of the drug is not required for its activity. When administered with fat containing foods, orlistat partially inhibits hydrolysis of triglycerides thus reducing the subsequent absorption of monoglycerides and free fatty acids. Thus Orlistat through lipase inhibition results in malabsorption of fats which leads to a reduction of body weight and cholesterol.

Orlistat's pharmacological activity is dose dependent. It exhibits an initial steep portion of the dose response curve followed by a subsequent plateau for doses above 400 mg/day. At therapeutic doses (120 mg/day tds with three main meals) administered in conjunction with a well balanced, mildly hypocaloric diet, the inhibition of fat absorption is approximately 30% of ingested fat. This contributes an additional caloric deficit of approximately 200 calories. Orlistat does not

affect the absorption and pharmacokinetics of drugs with a narrow therapeutic index such as phenytoin, warfarin and digoxin. However, at doses of 50 mg three times daily, orlistat alters the pharmacokinetics of antihypertensive drugs such as atenolol, furosemide, nifedipine and captopril to a clinically significant extent (20).

Clinical, double blind, placebo controlled trials have been conducted with Orlistat in obese subjects and in obese subjects with comorbid conditions such as diabetes, hypertension and coronary heart disease. Orlistat has been studied in about seven multicentric trials conducted for 1-2 years, where the experimental group was administered the drug in conjunction with a balanced, hypocaloric diet and the placebo group was treated by the same hypocaloric diet alone. These studies ultimately culminated in its approval by the FDA as an antiobesity drug. In the first year, studies revealed the following findings. Orlistat blocked the absorption of fat by about 30%. Overall a weight loss of >5% and >10% of initial body weight was observed in most of the subjects in the Orlistat group as compared to those in the placebo group. Also noted was a significant improvement of the lipid profile in the orlistat group, especially total cholesterol and LDL cholesterol. Amelioration of glycemic control in diabetic subjects i.e. fasting blood glucose and HbA1c was observed in the orlistat group as compared to the placebo group. About one third of the subjects in the orlistat group experienced gastrointestinal disturbances which were mild and transient. At the end of year one, the patients' diets were reviewed and weight maintenance diets were prescribed for the second year. In the second year, weight regain in the orlistat group was significantly less in a larger number of subjects than that observed in the placebo group. Thus weight control was better in the treatment group. However, reduction in the absorption of fat soluble vitamins has been shown. Hence, supplementation with fat soluble vitamins, especially vitamin E has been suggested in long term treatment (21-28). With high fat intake, use of Orlistat will expectedly result in lot of undigested, unabsorbed fat in the stool and resultant faecal soiling.

Thus, orlistat in conjunction with a reduced caloric diet is indicated for weight loss and weight maintenance. It is also indicated for treatment of obesity in the presence of other risk factors. The claims of efficacy of the drug, safety on continuous usage and its effect on morbidity and mortality is yet to be evaluated.

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