Carbohydrate metabolism and de novo lipogenesis in human obesity[1-3]

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ABSTRACT Respiratory exchange was measured during 14 consecutive hours in six lean and six obese individuals after ingestion of 500 g of dextrin maltose to investigate and compare their capacity for net de novo lipogenesis. After ingestion of the carbohydrate load, metabolic rates rose similarly in both groups but fell earlier and more rapidly in the obese. RQs also rose rapidly and remained in the range of 0.95 to 1.00 for ~8 h in both groups. During this time, RQ exceeded 1.00 for only short periods of time with the result that 4 ± 1 g and 5 ± 3 g (NS) of fat were synthesized via de novo lipogenesis in excess of concomitant fat oxidation in the lean and obese subjects, respectively. Results demonstrate that net de novo lipid synthesis from an unusually large carbohydrate load is not greater in obese than in lean individuals. *Am J Clin Nutr* 1987;45:78–85.

KEY WORDS Thermic effect, indirect calorimetry, substrate oxidation, substrate balance, obesity

Introduction

Obesity is caused by ingestion of food energy in excess of expenditure. To help in weight control, many regimens have been suggested with various permutations among the three energy-providing components in foods, ie, protein, fat, and carbohydrate (1). It is often advocated that carbohydrate should be reduced to a minimum (2), which suggests that conversion of carbohydrate into fat is often believed responsible for the increased fat deposition in obesity. Indeed, this view is supported by many animal models of obesity in which de novo lipogenesis is accelerated (3).

While de novo lipogenesis can be induced and demonstrated in adult man, for example during total parenteral nutrition (4), information concerning its contribution to human obesity is lacking. Bray et al (5) investigated lipogenesis in fat biopsies from five obese patients consuming a high- and a low-energy diet and demonstrated increased lipogenesis from glucose and pyruvate in the biopsies of those patients consuming a hypercaloric (3500 kcal) weight-gaining diet.

However, later studies have demonstrated that the capacity for human adipose tissue to convert glucose to lipid is very low (6–8) and it was suggested that the liver was the major site for de novo lipid synthesis (6). This was supported by Angel and Bray (9) and by Barter et al (7), who observed that glucose conversion to triglyceride fatty acid persisted for up to 12 h after the last meal in the liver biopsies of subjects primed with carbohydrate-rich diets. On the other hand, Björntorp and Sjöström (10) concluded that liver and intestine as well as adipose tissue had very limited lipogenic capacities.

In a previous study (11), we fed a very large (500 g) carbohydrate load to young, healthy, lean male volunteers to investigate the influence of the antecedent diet upon de novo lipogenesis; the net conversion of glucose to fat was found to be enhanced in subjects who had a carbohydrate-rich diet, though it remained very limited (9 ± 1 g). In the present study, we have used the same experimental protocol to investigate net de novo lipogenesis in a

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group of obese individuals consuming their habitual diet. The results are compared with those previously obtained in lean subjects of a comparable age and height.

Methods

Subjects

The physical characteristics of the six healthy, young, obese individuals (two females and four males) and of six matched lean controls are presented in **Table 1.** Except for one obese subject (#10) whose father had recently been diagnosed as diabetic, none of the obese or lean subjects had relatives with diabetes mellitus. None were on a weight-reducing diet nor were they receiving any medication at the time of the study. The experimental protocol was reviewed and approved by the University's ethical committee and explained in detail to the participants before they gave their informed consent.

Study design

The obese and lean subjects were consuming an ad libitum diet on which their body weights had remained stable. During the 3 days preceding the test, a eucaloric mixed diet containing 12% protein, 30% fat, and 58% carbohydrate was provided to the six lean subjects.

On the night before the test, subjects slept in a room adjoining that in which the experiment was to be performed. The subject was awakened at 0630 h and, after voiding, was weighed. A flexible venous catheter (Venflon® Viggo, Helsingborg, Sweden) was then placed in an antecubital vein and kept patent with physiological saline (0.9% NaCl).

With the use of a ventilated hood, continuous respiratory exchange measurements (12) were performed on the recumbent subject for 15 h, starting 1 h before the ingestion of the first portion (ie, one-half) of a 500-g dose of dextrin maltose (Roquette Frère, Lille, Cedex France) dissolved in 1.2 L water and flavored with fruit juice. The carbohydrate load was consumed in three portions: 250 g at zero time and 125 g, 2 h and 5 h later.

The respiratory exchange measurements were interrupted at 5 h and 10 h for a period of 30 min while the calibrations of the gas analyzers were verified, the subject's urine was collected, and his/her body weight was recorded. At 14 h, the subject was allowed out of the ventilated hood system but again spent the night at the Institute where his/her resting metabolic rate was measured for 1 h on the following morning.

Blood samples were taken every 30 min from −30 to 300 min and, thereafter, every hour until 14 h, at which time the catheter was removed. A final sample was taken at 24 h by venipuncture.

TABLE 1
Physical characteristics of subjects

Subjects	Sex	Age	Weight	Height	BMI
		yr	*kg*	*m*	*kg/m²*
		Lean subjects			
1	F	23	65.0	1.66	23.6
2	F	24	62.5	1.72	21.1
3	M	23	64.5	1.80	19.9
4	M	24	83.7	1.87	23.9
5	M	19	65.7	1.79	20.5
6	M	22	75.2	1.86	21.7
Mean		23	69.4	1.78	21.8
SD		2	8.3	0.08	1.6
		Obese subjects			
7	F	32	83.4	1.62	31.8
8	F	23	86.0	1.68	30.5
9	M	26	109.0	1.84	32.2
10	M	22	111.0	1.81	33.9
11	M	20	92.0	1.78	29.0
12	M	22	95.0	1.86	27.5
Mean		24	96.1	1.77	30.8
SD		4	11.6	0.10	2.3

Analyses

Blood samples were analyzed for glucose (13), insulin (14), free fatty acids (15) on the Dole extract (16), and blood-urea nitrogen (17).

Data analysis

Oxygen consumption and carbon dioxide production are presented as integrated values over 30-min periods. Rates for the periods when the subjects were not being measured were obtained by interpolation. Urine collected at the beginning, during, and at the end of the test was analyzed for nitrogen (18). After correction for changes in blood-urea nitrogen during the test, the average rates of protein oxidation were calculated.

Changes in the subjects' carbohydrate and lipid contents were calculated from the nonprotein respiratory quotient (NPRQ) as described elsewhere (11, 19). We determined metabolic rates taking into account the energy equivalent of the oxygen consumed during protein oxidation. NPRQs > 1.0 were taken to indicate that lipogenesis exceeded fat oxidation, and the amount of lipid gained during such periods (ie, *net lipogenesis*) was calculated as already described (11).

We calculated the thermic effect of the dextrin-maltose load by dividing the increase in resting metabolic rate above the postabsorptive resting metabolic rate by the energy content of the dextrin maltose consumed. The gross energy content of the dextrin maltose was analyzed by bomb calorimetry (Parr Instruments, Cambridge, UK), ie, 4.1 kcal/g anhydrous dextrin maltose, and was added to the energy provided by the fruit juice (20).

"Student's" unpaired t test was used to perform statistical analyses. Results are presented as means ± SEM unless stated otherwise.

Results

Blood-sample variables

The changes in circulating glucose, insulin, and free fatty acid (FFA) concentrations are shown in **Figure 1.** Basal values were slightly higher in the obese group for all three variables,

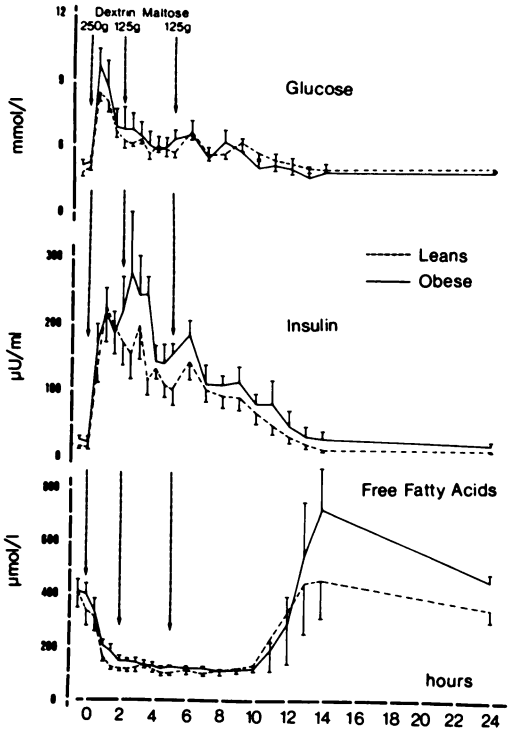

FIG 1. Changes in glucose, insulin, and free fatty acids in blood samples from the two groups after ingestion of 500 g dextrin maltose.

but none were significantly different. After the first carbohydrate load, blood glucose rose to peak values of 8.4 ± 0.5 and 9.6 ± 0.7 mmol/L (NS) at 30 min and then declined progressively throughout the test. Insulin concentrations also rose, reaching peak values at 60 min, ie, 228 ± 55 μU/mL in the leans and 217 ± 35 μU/mL in the obese.

After the second dextrin-maltose load, insulin rose further to 275 ± 91 μU/mL in the obese, whereas it remained below the 60-min value in the lean subjects. Subsequently, insulin concentrations decreased similarly in both groups, reaching baseline concentrations after 14 h. On the next morning, insulin concentrations were the same as the day before.

Fasting plasma-FFA concentrations were not different between the two groups (413 ± 67 μmol/L in the leans and 412 ± 41 μmol/L in the obese). After the dextrin maltose was ingested, FFA concentrations decreased, reaching plateaus of ~130 μmol/L at 120 min in both groups, and remained at this value until 10 h. As insulin decreased to baseline values, the FFAs increased gradually to concentrations exceeding the baseline values, ie, 456 ± 149 and 721 ± 153 μmol/L in the lean and obese subjects, respectively.

Energy expenditure and respiratory quotient

The postabsorptive resting metabolic rate was 1.49 ± 0.10 kcal/min in the obese and 1.28 ± 0.10 kcal/min in the leans. The changes in metabolic rate in response to the dextrin-maltose load are shown in **Figure 2.** The increase in metabolic rate was of the same order during the 5.5 h after the first carbohydrate load. Afterwards, the metabolic rate decreased more rapidly in the obese group, reaching baseline value at 10.5 h. It rose to 1.57 ± 0.14 kcal/min at 90 min in the lean group, remained at ~1.5 kcal/min for a further 7.5 h, it then decreased but was still slightly above baseline value at 14 h. Thus, the thermic effect of the carbohydrate load was less in the obese (4.3 ± 0.6%) than in the lean group (7.4 ± 0.7%, $p < 0.01$).

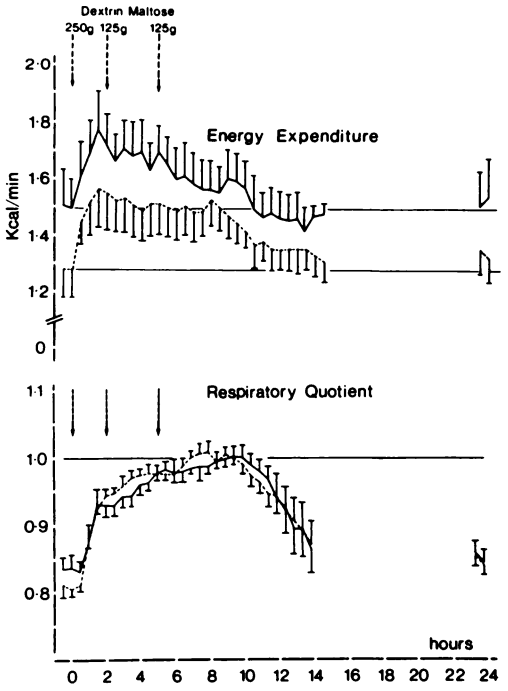

FIG 2. Changes in the energy expenditure and the respiratory quotients of the lean (- - - - -) and obese (——) subjects after ingestion of 500 g dextrin maltose.

Changes in the respiratory quotient (RQ) are illustrated in the lower section of Figure 2. During the baseline period, RQs were slightly lower in the lean (0.804 ± 0.011) than in the obese (0.836 ± 0.020) group. After the carbohydrate load, the RQ rose rapidly in both groups and exceeded 0.95 at 2.5 h in the lean, and at 3.5 h in the obese subjects. RQs of both groups remained above this value for a further 8–8.5 h. During this time, the mean nonprotein RQ exceeded 1.00 for short periods of time, which corresponded to periods of net de novo lipid synthesis (*see Substrate oxidation*). About 10–11 h after ingestion of the carbohydrate load, RQs fell similarly in both groups but remained above baseline values at 14 h (0.870 ± 0.034 in the lean and 0.864 ± 0.036 in the obese).

The next morning, the average postabsorptive RQs were slightly higher than the day before in both the lean (0.804 ± 0.011 vs 0.847 ± 0.015, NS) and obese (0.836 ± 0.020 vs 0.852 ± 0.016, NS) subjects, but they were not significantly different.

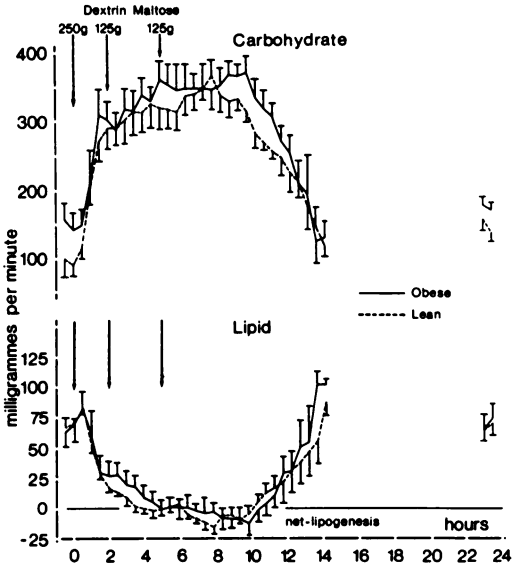

FIG 3. Carbohydrate and lipid utilization in the two groups after ingestion of the carbohydrate load. Negative values for lipid oxidation represent net de novo lipid synthesis.

Substrate oxidation

In the postabsorptive state, carbohydrate oxidation was 101 ± 30 mg/min in the lean and 157 ± 23 mg/min in the obese group (NS). Upon ingestion of the load, carbohydrate disappearance (which includes glucose oxidation and glucose transformed into lipid) increased similarly in both groups (**Fig 3**), attaining rates of 300–350 mg/min at 2–2.5 h after the first ingestion. These rates were maintained for a further 9 h. Carbohydrate oxidation then decreased rapidly and returned to basal rates at 14 h. Postabsorptive fat oxidation was also similar in the two groups (~75 mg/min) and decreased after carbohydrate ingestion.

Lipid synthesis exceeded lipid oxidation (ie, net de novo lipogenesis) after 4 h in the lean and 5 h in the obese subjects and continued to do so, albeit at a low rate, for a further 5.5 h in both groups. From then on, lipid oxidation increased and exceeded synthesis; after 14 h, lipid oxidation returned toward the rates observed in the postabsorptive state (55 ± 19 and 101 ± 10 mg/min in the lean and obese, respectively). Postabsorptive carbohydrate- and lipid-oxidation rates on the next morning were similar to the values measured on the preceding day.

Figure 4 (a) illustrates the fate of the 500 g of dextrin maltose (497 ± 2 g and 500 ± 1 g in the lean and obese groups, respectively) 14 h after its ingestion. The lean subjects oxidized 223 ± 10 g and the obese, 240 ± 15 g (NS) of carbohydrate. During the periods when the nonprotein RQ exceeded 1.0, a cumulated amount of 13 ± 5 g and 16 ± 9 g of carbohydrate were used for net de novo lipogenesis in the lean and obese, respectively (NS). The remaining 260 g in both groups was stored as glycogen.

The substrate balances of the two groups at 14 h are presented in Figure 4 (b). During the 14 h, the lean subjects oxidized 28 ± 4 g protein and 15 ± 4 g of fat. Of the 15 g of fat oxidized, 4 ± 7 g were restored by synthesis from carbohydrate, resulting in an overall balance of −11 ± 4 g.

In the obese, 29 ± 3 g of protein were oxidized during the 14 h. The total amount of fat oxidized was similar to that of the lean controls (19 ± 5 g/14 h) and was counter-balanced by a gain of 5 ± 3 g of fat during the periods in which de novo synthesis of fat exceeded concomitant fat oxidation. This resulted in an overall fat balance of −14 ± 8 g/14 h.

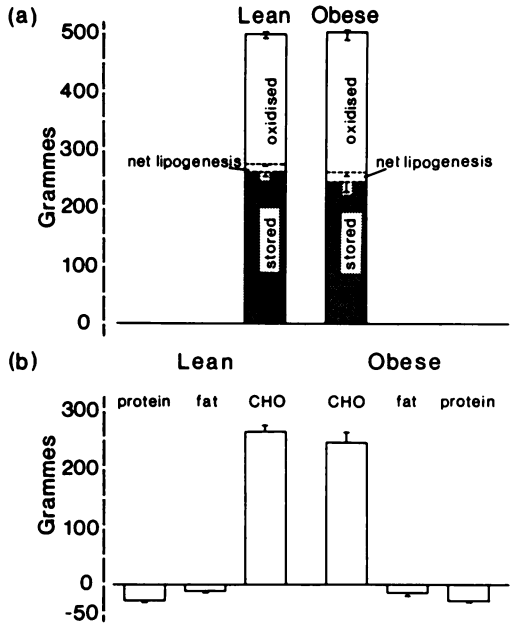

FIG 4. (a), Metabolic fate of 500 g dextrin maltose in the lean and obese subjects 14 h after ingestion of the test meal. (b), Protein, fat, and carbohydrate (CHO) balances in the lean and obese subjects 14 h after ingestion of the test meal.

Discussion

In young, lean subjects, ingestion of very large carbohydrate loads (ie, 500 g) is accommodated primarily by increases in the body's glycogen stores, without any increment in the body's fat content (19). This is because the rate of de novo lipogenesis is not sufficient to compensate for concomitant fat oxidation, except during brief periods (11, 19). The amount of fat that is synthesized in excess of fat oxidation during these periods varies, depending on the composition of the preceding diet, presumably because the degree of replenishment of the body's glycogen stores at the time of consuming a 500-g carbohydrate load is influenced by the diet's carbohydrate content.

Using the present data, we were able to assess and compare carbohydrate conversion to glycogen and into fat as well as the thermogenic response in obese and lean subjects who had ingested 500 g of dextrine maltose. All subjects participating in these studies were maintaining a stable body weight while consuming the usual, mixed Western diet. The lean subjects were participating in studies involving the consumption of different diets during the days immediately preceding the tests. The data used for the present comparison were obtained after these subjects had consumed a mixed diet in which protein accounted for 12%, fat for 30%, and carbohydrate for 58% of its energy content for the past 3 days.

Indirect calorimetry permits the calculation of changes in the body's protein, carbohydrate, and fat contents (21). As illustrated in **Figure 5**, the body's total fat content decreased at a much slower rate following ingestion of the carbohydrate load in both obese and lean individuals when compared with subjects who continued fasting. After 14 h, body-fat balances were -14 ± 8 g and -11 ± 4 g in the obese and lean, respectively, values that were already less than those of subjects who had fasted for only 5 h (-21 ± 1 g).

Five hours after subjects ingested the last portion of the 500 g of maltodextrin, the blood-glucose level had returned to baseline values (Fig 1). Assuming that carbohydrate absorption was by then completed, glycogen levels had increased by 306 ± 14 g in the obese and 315 ± 13 g in the lean subjects. This is consistent with earlier indirect calorimetry studies of Passmore et al (22) who observed very little net lipogenesis in two obese women overfed a high-carbohydrate diet. These authors also concluded that most of the carbohydrate is stored initially as glycogen, perhaps to be used subsequently for de novo lipogenesis. The storage capacity in man is thus sufficient to accommodate increments in glycogen that exceed by far the amounts of carbohydrate commonly consumed in a mixed diet. Even after an exceptionally massive intake of carbohydrate, the rate of de novo lipogenesis remains too low to compensate for the fat oxidation that occurs between meals. This indicates that there is little need and opportunity for substantial carbohydrate conversion to fat while a mixed diet is consumed.

Although the disposal of the carbohydrate load appeared to proceed similarly in obese and lean individuals, an appreciable difference in their thermic responses to the dextrin-maltose load was apparent. The increments in energy expenditure above the baseline rates

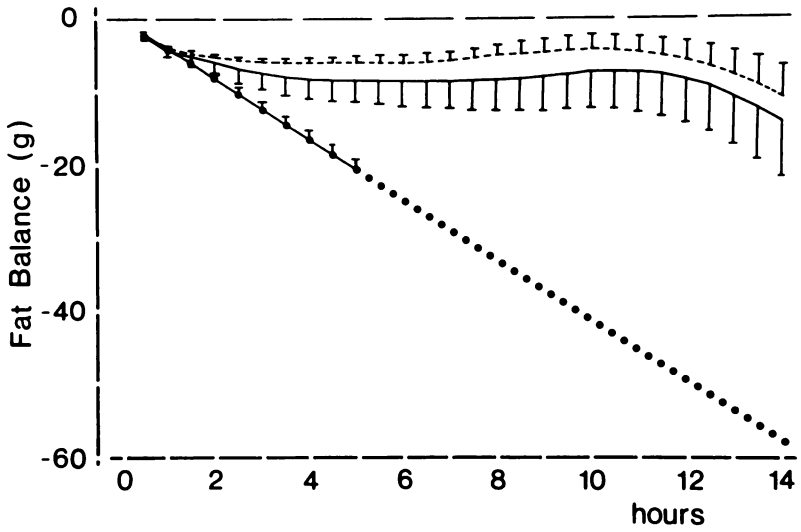

FIG 5. Cumulative fat balance in the lean (- - - - -) and obese (——) subjects during the 14 h after the test meal, compared with five control subjects (● —— ●) who remained fasted for 5 h.

amounted to 151 ± 15 and 89 ± 12 kcal in the lean and obese subjects, corresponding to 7.4 ± 0.7% and 4.3 ± 0.6% of the energy taken in, respectively.

This effect was clearly evident in one of the obese subjects (#10, son of the diabetic father) whom we were able to study again after an 11-mo interval, during which he achieved a weight loss of 35 kg. When first studied, his observed thermic effect was 4.3%; it almost doubled, reaching 8.2%, after the weight loss. Net lipogenesis was increased as well, from 0 to 5.7 g.

Low thermogenic responses to glucose or to mixed meals have often (23–26), but not always (27–30), been observed in groups of obese subjects. Although the thermic effects of the dextrin-maltose load were lower in the obese than in the lean individuals at all times, they did not become significantly different until 8 h after ingestion of the first load of carbohydrate. Our data clearly show how important it is to follow the metabolic response until resting energy expenditures have returned to the premeal baselines rates, particularly when attempting to compare the thermic effect of food among different groups of subjects. In spite of their lower thermic response, however, the total energy expenditure was slightly greater in the obese than in the lean subjects (1300 ± 87 vs 1224 ± 77 kcal/14 h, NS) on account of their higher resting metabolic rate (1.49 ± 0.10 vs 1.28 ± 0.10 kcal/min).

The lower thermic response to an influx of carbohydrate has recently been attributed to the occurrence of insulin resistance in obesity, and insulin resistance was therefore considered to be a possible factor contributing to the development and/or maintenance of obesity (24). However, when glucose uptakes in lean and obese individuals were made comparable by increasing the insulin infusion rate in the obese subjects during glucose-clamp studies, the thermic effects became identical, suggesting that the thermic effect is related primarily to the rate of glucose storage rather than to an effect of insulin resistance on thermogenesis (31).

Respiratory exchange measurements can be used to establish changes in the body's protein, carbohydrate, and fat contents but cannot detect to what extent fatty acid synthesis may have occurred in one body compartment while a like amount of fatty acids was oxidized in other tissues. If such *hidden lipogenesis* were to occur at a higher rate in the lean subjects during the last 4 h of the test, the high metabolic costs required for this process (32) could explain, at least in part, the difference in the thermic responses that became manifest toward the end of the test. The synthesis of 25 g of fat from carbohydrate (compensated

by the oxidation of 25 g of fat elsewhere in the body) would be required to account entirely for the difference. To what extent this, or an alteration in the catecholamine-mediated component of the thermogenic response (33) may be involved cannot be resolved from our data.

The present results indicate that accumulation of adipose tissue fat is not due to an increase in de novo fat synthesis from carbohydrate in moderately obese subjects consuming a high-carbohydrate meal; hence, a mixed diet is even less likely to increase de novo fat synthesis. This is consistent with the work of Hirsch (34) who demonstrated that the fatty acid pattern in adipose tissue triglycerides reflects the type of dietary fat consumed.

Carbohydrate intake remains an important factor because it favors the accumulation of dietary fat in adipose tissue by reducing the rate of exogenous fat oxidation (Fig 5). This is particularly the case inasmuch as carbohydrate oxidation increases promptly after food intake while fat oxidation is inhibited. This metabolic response is important in helping the organism to maintain carbohydrate balance, but it prevents an equivalent phenomenon in the case of fat—the ingestion of lipids does not promote postprandial fat oxidation (21). Fat balance is thus essentially equal to the discrepancy between fat intake and fat oxidation (which is determined by the energy gap between carbohydrate-plus-protein intake and total energy expenditure).

Evidence that dietary fat, rather than fat synthesis from carbohydrate, provides the precursors for adipose tissue triglycerides should help to alleviate the commonly held fear among weight-conscious individuals that carbohydrate turns into fat. This erroneous belief may lead these individuals to avoid foods known to contain primarily carbohydrates in favor of foods known for their low-carbohydrate content (ie, high-protein items). Such a pattern of food selection would be unfortunate, indeed, because it promotes the consumption of foods with a high-fat content, which is much more likely to sustain a positive fat balance than dietary carbohydrate.

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