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Dietary fat, lipogenesis and energy balance

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Abstract

Today, there are still uncertainties about the role of exogenous fat on body fat regulation. Early models of energy utilization (for example, Kleiber's, early 20th century) failed to take into account the nature of substrate oxidized in the control of food intake, whereas more recent models (e.g., Flatt's model, end of 20th century) did. Excess body fat storage is ultimately a problem of chronic positive energy balance mediated by a poor control of energy intake or/and a blunted total energy expenditure. Excess fat storage can stem from exogenous fat and to a more limited extent by nonfat substrates precursors transformed into body fat, mostly from carbohydrates, a process known as de novo lipogenesis. When considered over periods of weeks, months or years, total fat balance is closely related to energy balance. Over periods of days, the net change in fat balance is quantitatively limited as compared to the size of endogenous fat storage. The issues discussed in this article primarily include the stimulation of de novo lipogenesis after acute or prolonged CHO overfeeding and whether de novo lipogenesis is a risk factor for obesity development.

Keywords: Lipogenesis; Fat balance; Energy expenditure

1. Introduction

With the advent of molecular biology, the concept of fat balance has tended to be slowly overshadowed, although it has a long history in animal and human physiology and it remains true no matter what disturbance is found at the molecular level. Its accurate assessment outside the laboratory, in free living conditions has plagued nutritionists for a long time. In confined conditions, the study of fat balance in man has been carried out for some decades, using a large respiration chamber [25,29,32], i.e., in conditions similar to what has been used for farm animals (comfort added to it!). The use of indirect calorimetry [31] has been of primary importance to explore the etiologic factors related to obesity [27] and to explore the determinants of fat oxidations in adults [20,26] and children [17].

The purpose of this article is to review the concept of fat balance, to further refine it and to explore to what extent de novo lipogenesis from carbohydrates substantially affects daily fat balance.

In a respiration chamber, fat balance equation is generally calculated over a period of 24 h or more. This reflects static conditions and it is expressed as:

$$\text{Fat balance (static)} = \text{total metabolizable fat intake} - \text{whole body fat oxidation} \quad (1)$$

Negative balance leads to body fat loss. Positive fat balance leads to body fat gain and obesity can only result from a chronic state of positive fat balance. Here, for the purpose of simplicity, fat oxidation is considered separately from CHO balance, but one should realize that fat and CHO oxidation are not mutually independent and there is an intimate interrelationship between them [11]. Indeed, in isocaloric conditions, at a fixed energy expenditure level and keeping protein intake constant, there is a precise inverse relationship between CHO and fat oxidation: the greater the proportion of CHO oxidized, the lower the proportion of fat oxidized.

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Obesity develops during a dynamic phase during which fat balance remains positive for a prolonged period of time (Fig. 1). However, this process is not necessarily sequentially on consecutive days: positive fat balance on one day may be partially compensated (or not) by negative fat balance on subsequent days. What counts is the cumulative effect!

A new equilibrium is eventually reached after several months, or years depending upon several factors which include the magnitude of fat imbalance and initial body fat [34], the more excess fat in the body, the more time it will take to reach equilibrium and the more weight will be gained. Ultimately, the slow rise in whole body fat oxidation with time (accounted for by increased energy expenditure) will match the step rise in fat intake. Note that at middle and long term, energy balance is closely related to fat balance as we have shown in our laboratory [25] and more recently as published by Schrauwen et al. [23]. This is illustrated in Fig. 2.

In the dynamic phase of weight change, what is of interest is to calculate the change (Δ) in fat balance:

$$\Delta \text{ fat balance (dynamic)} = \Delta \text{ total metab. fat intake} - \Delta \text{ whole body fat oxidation} \quad (2)$$

This equation indicates that a change in fat balance can be mediated by a change in metabolizable fat intake or a change in fat oxidation or both situations combined.

As illustrated in Fig. 1, the rise in endogenous fat storage accompanying a prolonged increase in fat intake, progressively leads to an enhanced fat oxidation in the dynamic phase of weight gain up to a reequilibrium in fat balance.

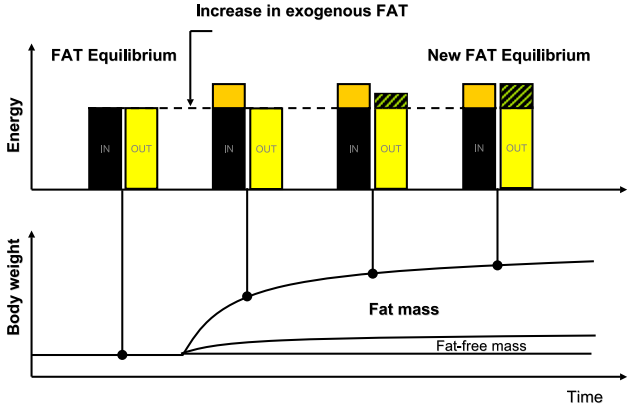

Fig. 1. Dynamic change in fat balance following a step increase in exogenous fat. The time required to reach a new equilibrium in fat balance is very long (years) and depends upon the extent to which fat oxidation increase with increase fat storage, the latter being individually determined by endogenous (genetic predisposition) and endogenous factors. Note that 10 kg of excess body fat increases fat oxidation by (only!) 20 g per day so that if an excess fat of about 180 kcal (20 g) is ingested at time zero, the gain in body fat to offset this excess is approximately 10 kg gain of adipose tissue!

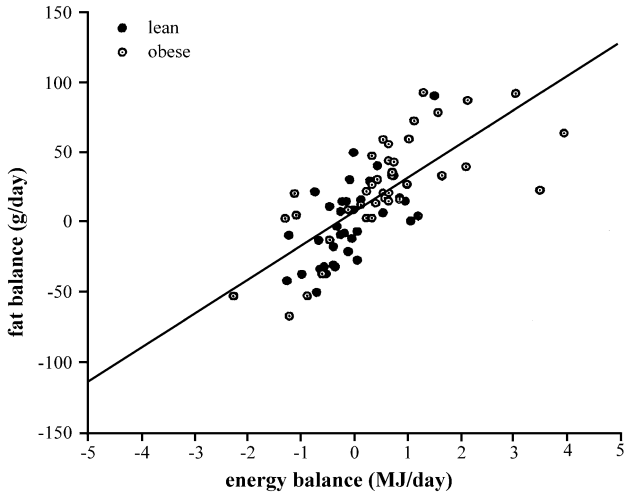

Fig. 2. Relationship between energy balance and fat balance in lean and obese individuals (data from Schrauwen et al. [23]). Note that at zero energy balance, fat balance is zero. At an excess or deficit of 4.2 MJ/day (1000 kcal), the fat balance (about 100 g/day=900 kcal/day) account for more than 90% of the magnitude of energy balance.

2. Control of energy and substrates output: new and old models

How can the various components of the body balance be represented to account for the variation in the regulation of fat vs. carbohydrate utilization by the body? Many human models on energy metabolism have been developed over the last decades and all cannot be listed here (e.g., Ref. [18]). Human models are not only of interest for pedagogic purposes. The usefulness of models, in particular if they are quantitative, is that the nature and the relative importance of various endogenous and exogenous factors on the outcome variable as well as their interactions can be approached in an organized and simplified way. It seems warranted to recall a classical model by the Swiss pioneer in energy metabolism Kleiber [15] in the beginning of the 20th century for several reasons: (a) it is still of interest today, (b) it has a strong historical background particularly in animal physiology and nutrition and (c) it has formed the basis of subsequent models in human physiology. The model was based on a hydraulic system (Fig. 3). It clearly demonstrates three important concepts: (1) the metabolic loops in the control of energy utilization, (2) the various sources of energy losses in the body (i.e., intestinal energy losses, losses in thermogenic processes) and (3) the endogenous and exogenous factors influencing energy expenditure and fuel utilization for maintenance, growth and milk production.

Fifty years later, Flatt [9,10] also used a hydraulic system, in which the effect of gravity (or hydrostatic pressure) is illustrated to demonstrate his hypothesis about the control of substrate utilization (Fig. 4). Obviously, the

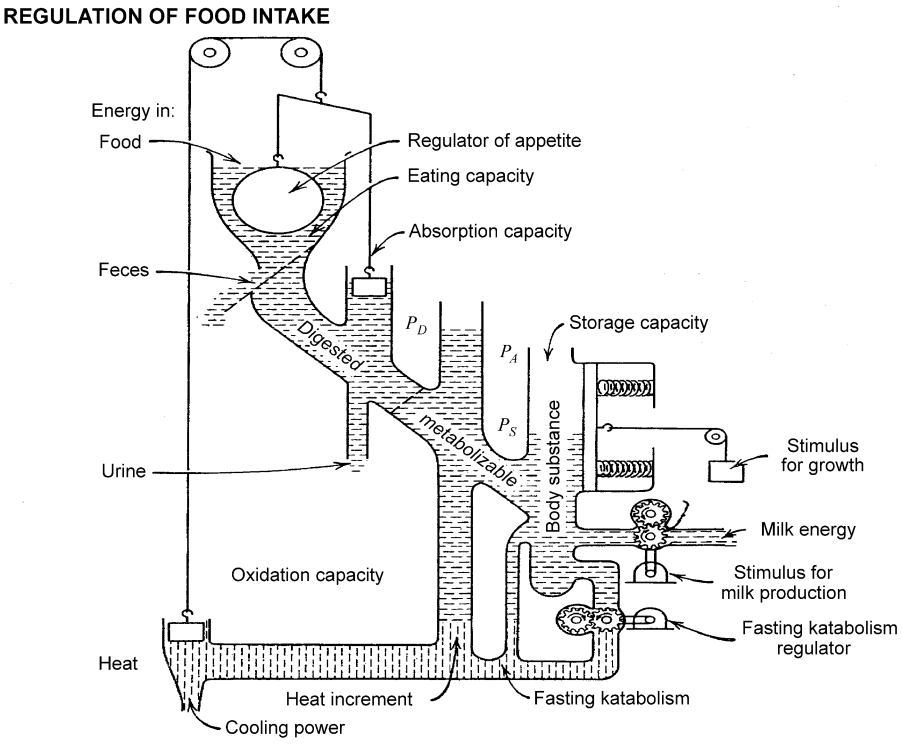

Fig. 3. Hydraulic model of Kleiber [15] showing the different sources of energy losses from the body (intestinal losses, postprandial thermogenesis called "heat increment") and the feedback loop to the control of food ingestion through appetite and via the rate of total energy output.

research accumulated between the early 20th century (Kleiber's model) and the late 20th century (Flatt's model) brought many new information on fuel metabolism in humans. A major difference between Flatt's model and the classical one is that the former expresses the fuel control of the body as macronutrient rather than energy. Indeed, the body has no known mechanism to detect the energy entity as such. Many post-Flatt models failed to adequately take into account substrate competition in the partition of nutrients oxidation flux.

It seems important to detail the basis of the model of Flatt [9,10], which has the merit of highlighting the interactions of macronutrients (in particular CHO and fat) in a semi-quantitative way.

A shown in Fig. 4, a small and large reservoir illustrates the human bodies' limited capacity for body storage and oxidation of carbohydrate and of fat and their various partition in their oxidation rate. Glucose and free fatty acid oxidations are assumed to be proportional to the levels at which the two reservoirs are filled at a given time. This is the essence of Flatt's hypothesis.

The food consumption is determined by the factors regulating the pattern of meal consumption and by physiological mechanisms, which assure that glycogen levels and reserves are sufficient to avoid hypoglycemia and to prevent their build-up to excess levels, which would induce de novo lipogenesis. In the model, this is visualized as a connection between the small reservoir to the large one. The interplay between such variability in fuel utilization and the factors controlling food intake results in the up and down oscillation of glycogen levels within a particular operating range. In a situation in which outflow from the large reservoir (representing fat oxidation) is not equal to inflow (representing fat intake), its content (representing adipose tissue mass) will slowly drift over time. Because of the increase in the level of the large reservoir, its outflow will increase until it is equal (on average) to the amount of fuel added to it, so that steady state (representing weight maintenance) will then be reached. In summary, according to Flatt's view, individuals are pushed towards a particular body composition for which their glycogen reserves and adipose tissue mass drive metabolic fuel regulation in such a way as to bring about the oxidation of glucose and fatty acids to closely match the proportions of carbohydrates and fat in the diet.

Note that models should be constantly updated with the acquisition of new knowledge and the relative importance of models is immense didactically but their importance are generally fading out with decades because, in the case of Flatt's model, consistent scientific evidence in the human literature is still lacking in particular when studies are independently carried out. Taken together, we can infer that stable body weight and body composition can only be maintained if the amount and composition of metabolic fuel mixed oxidized matches the macronutrient mixture ingested. Since body weight must be stable, not from day to day, but on average over a certain period of time, appropriate corrections are required by metabolic and behavioral factors to avoid a positive drift in body composition, in particular of

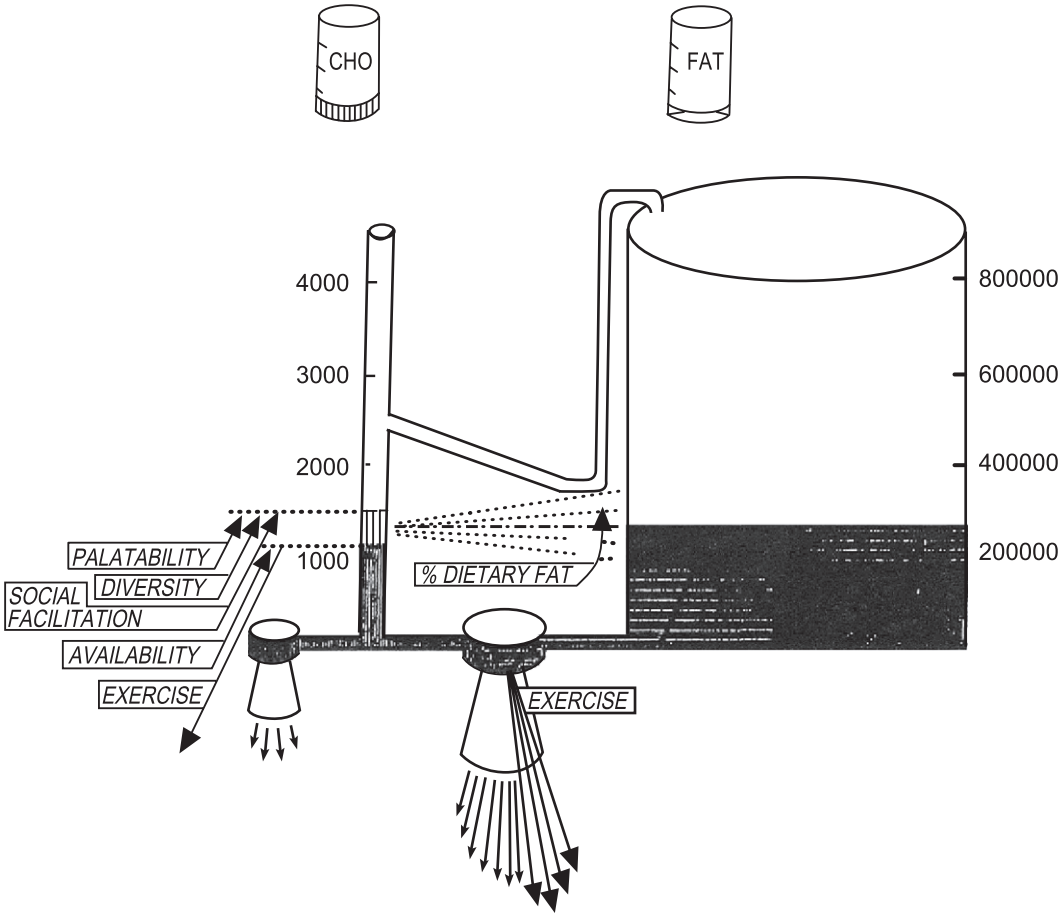

Fig. 4. Hydraulic model of Flatt [9,10], which is constituted by 2 reservoirs, a small and large one, describing that limited capacity of the body for storing glycogen (a few hundred grams) and the large capacity for storage fat (a few decakilos), respectively. There is a small turbine, which represents the exclusive use of glucose by the brain (approximately 100 g/day). The relative proportions of glucose and fatty acids used by the body (brain excluded) is represented by the large turbine and is assumed to be influenced by the proportional availability of glucose and free fatty acids. Replenishment of the body's glycogen and fat stores occurs from time to time by the exogenous supply of macronutrients (meal ingestion). The fraction corresponding to the dietary fat content is therefore delivered into the large reservoir. Addition of fuel from the meals to the large reservoir cause only a small change in its level, whereas marked changes in the content of the small reservoir occurs because of its small size. This engenders the rate of glucose oxidation to rise after meals and to adjust itself to glycogen availability of the body.

fat storage. This is the key feature in the dynamic control of body weight and body fat.

3. Does de novo lipogenesis influence fat balance?

The term lipogenesis refers to the biosynthesis of lipids. De novo lipogenesis indicates that the synthesis of fatty acids occurs from various nonfat precursors, mainly from glucose but also from amino acids and ethanol, i.e., from substrates, which produce acetyl-CoA during their catabolism and are therefore susceptible to be converted to fatty acids in the intermediary metabolism. Only the process of de novo lipogenesis from CHO will be discussed here, not that related to alcohol as in a previous review [28]. Note that there is also some new challenging ideas that claim that de novo lipogenesis may occur in muscle, in addition to the liver and the adipose tissue.

In the model of Flatt [9,10], de novo lipogenesis is taken into account: it diverts carbon atoms to fat tissue just as a sort of "sink" process. According to Flatt, this process plays little role in the regulation of carbohydrate balance, since under habitual feeding conditions, glycogen levels may remain relatively low and therefore they do not induce appreciable rate of lipogenesis.

The site of de novo lipogenesis is thought to be mostly the liver. In fact, the exact site of fatty acid synthesis has not be clearly determined in humans. The fact that the key enzymes involved in fatty acid biosynthesis are present in both the liver and adipose tissue suggests that the latter contribution may not be negligible [1]. Furthermore, the proportion of de novo lipogenesis accounted for by liver vs. adipose tissue in different nutritional conditions remains to be further investigated.

The fate of ingested CHO (exogenous origin) is well known. After intestinal absorption, CHO are partly oxidized and partially stored as glycogen in the liver and the muscles for subsequent use in the postabsorptive period. If large amounts of CHO are ingested over a prolonged period of

time, some CHO will be converted progressively to fat by de novo lipogenesis. An excellent review on the metabolic and regulatory aspects of de novo lipogenesis in humans has been published by Hellerstein [12].

The different nutritional conditions under which de novo lipogenesis has been investigated in healthy individuals include:

(a) Acute study: single massive CHO load (i.e., in our laboratory, Refs. [2–4])
(b) isoenergetic high-CHO–low-fat diets [8,14]
(c) hyperenergetic high-CHO–low-fat diets with ad lib vs. controlled diets [16,22] and fixed vs. progressive overfeeding [24]
(d) the effect of potentially lipogenic substrates (e.g., glucose, fructose and saccharose) [12]
(e) The effect of alcohol [31].

The individual's characteristics studied include the effect of excess body fat (e.g., obesity) and the effect of gender and menstrual cycle.

3.1. How is de novo lipogenesis estimated?

The techniques which have been developed to assess de novo lipogenesis include indirect calorimetry, tracer studies (stable nonradioactive isotopes, such as heavy carbon or heavy water) as well as much more indirect estimates based on changes in body composition in conjunction with the sequential assessment of whole body nutritional balances (Table 1).

Indirect calorimetry measures oxygen consumption (VO2) and carbon dioxide production (VCO2). The principle of the method is that when fatty acid is synthesized from glucose, such as following acute loads of CHO, the (nonprotein) respiratory quotient (RQ=VCO2/VO2) surpasses the value of 1.0 (=RQ of carbohydrates). From stoichiometric calculations, we know that 1 mol of palmitate (C16) synthesized de novo requires 4.5 mol of glucose (C6). Four moles of O_2 are consumed and 11 mol of CO_2 are released in this process. As a result, the RQ of the transformation is very high (2.75, i.e., 11/4), explaining why it can push up the RQ above 1.0.

Indirect calorimetry tracks de novo lipogenesis only when fat synthesis it exceeds concomitant fat oxidation. It does not assess the actual rate of de novo lipogenesis.

In the early 1990s a novel isotopic method called "mass isotopomer distribution analysis" (MIDA) has been developed by Hellerstein [12] to assess hepatic de novo lipogenesis, based on monitoring the rate of incorporation of ^{13}C labeled acetate into VLDL-palmitate synthesis. With this new method, it was shown that the fraction of glucose carbon atom converted into fatty acids in the liver depends upon the proportion of CHO in the antecedent diet. When expressed in absolute value, the amount of palmitate synthesized by the liver and released as VLDL triglycerides was relatively limited (i.e., a few grams per day).

Table 1
Methods used to assess "de novo" lipogenesis in humans

Methodology	Basic principles
(1) Continuous indirect calorimetry (Canopy)	Nonprotein respiratory quotient > 1.0 (without pulmonary hyperventilation), over given period of time, constitutes an index of whole body net lipogenesis.
(2) Tracer studies using stable isotopes	
(a) Mass isotopomer distribution analysis(MIDA)	De novo hepatic lipogenesis is assessed based on the pattern of labeling in the fatty acid molecules synthesized, which gives an indication of the precursor-pool enrichment analysis (MIDA) using combinatorial probabilities.
(b) Heavy water ($^2H_2$ ^{18}O)	The fractional biosynthetic rate is estimated from incorporation of $^2H_2$ derived incorporation from total plasma water pool into triglyceride-fatty acids.
(3) Whole body substrate balance associated with body composition	(a) Body fat storage in excess of total exogenous fat intake (during CHO overfeeding) suggests de novo fat synthesis (calculated by difference between increase total body fat minus exog fat)
	(b) Body fat storage without fat in the diet (i.e., during high CHO overfeeding) suggests de novo fat synthesis (calculated from net increase in total body fat)

An alternative tracer method estimates the fractional biosynthetic rate from the incorporation of deuterated water (D2O) derived from total plasma water pool into triglycerides.

Technically, measuring whole body total de novo lipogenesis in man is difficult and the different techniques measure different things: indirect calorimetry assesses lipogenesis at the whole body level but total lipogenesis is not measured only net values. In contrast, MIDA measures the rate of lipogenesis in one organ only (adipose tissue excluded), i.e., the liver. Obviously, the combination of both techniques appears to be very useful [19]. For example, in a study of massive CHO overfeeding, an index of adipose tissue lipogenesis was obtained by calculating the difference between whole body net fat synthesis (assessed by indirect calorimetry) minus hepatic lipogenesis (measured by MIDA). It was estimated, under these extreme conditions, that only 2% of the whole body net lipogenesis was accounted for by hepatic metabolism [1].

In summary, body fat storage can be derived from two major sources: (1) exogenous (dietary) fat stored in adipose tissue with a high energetic efficiency (98–99% of food energy) and (2) de novo fat biosynthesis produced from exogenous sources (mainly carbohydrates) with a low energetic efficiency (70–75% of food energy). The key issue is whether or not obesity (at least some form of obesity) may be associated to an increase in de novo lipogenesis?

Let us reconsider the classical fat balance in the light of the process of de novo lipogenesis.

When de novo fat synthesis occurs, we have to consider a new qualitative description of fat balance:

$$\text{Fat balance} = (\text{Exogenous fat intake} + \text{endogenous fat synthesis}) - (\text{exogenous} + \text{endogenous fat oxidation}) \quad (3)$$

Exogenous fat oxidation corresponds to the proportion of total fat oxidation accounted for by exogenous sources (i.e., fat in the diet). This is assessed by the use of exogenous fatty acids labeled with C13 and integrated in the meal [17]. Since exogenous fat in the postprandial phase is mostly stored (in adipose tissue), this fraction is generally low ranging from 10% to 20%, depending upon the conditions of measurements (duration) as well as the composition of the diet. Endogenous fat synthesis corresponds to the process of de novo lipogenesis from CHO. If we ingest massive hyperenergetic loads of CHO without exogenous fat, the fat balance equation simplifies to:

$$\text{Fat balance} = \text{Endogenous fat synthesis} - \text{Endogenous fat oxidation} \quad (4)$$

This is because exogenous fat intake and exogenous fat oxidation are both zero. Note that this "endogenous" fat balance precisely corresponds to net de novo lipogenesis assessed by indirect calorimetry. When both sides of the equation are identical, there is no net de novo lipogenesis and the NPRQ is equal to 1.0 [30]. This equation indicates that, if no exogenous fat is ingested, in order to be in positive fat balance and to gain body fat, total de novo fat synthesis must be greater than endogenous fat oxidation and this is precisely what happens with massive prolonged CHO overfeeding.

4. High-CHO diets and the drive for de novo lipogenesis

The classical intervention study is to acutely change the proportion of CHO in the diet [24]. Consecutive to a switch from a mixed- to a high-CHO diet, there is an acute increase in body weight which is transitory and which is explained by an increase in the size of the glycogen water-pool. The laymen, generally ignoring the concept of body composition, wrongly believe that the person has initially gained body fat. The popular assertion that high-CHO diets make you "gain weight" should be distinguished from "fat gain". More recently, the opposite view has been popularized, i.e., that all CHO ingested are automatically burnt out by the body, no matter what its absolute and relative levels in the diet. In fact, both of these concepts are erroneous as will be demonstrated. In fact, what is the real quantitative importance of net de novo lipogenesis in man?

More than 20 years ago, the late Bjorntörp and Sjostrom [6] have pointed out that, even with high isocaloric CHO meals, de novo lipogenesis was a quantitatively minor process in obese and nonobese individuals maintaining body weights. Yet, several investigators, based on animal data, believe that de novo lipogenesis constitutes a mechanism by which substantial fat accumulation can occur in humans [8].

In order to assess the effect of food intake on the magnitude of de novo lipogenesis, two situations must be considered, in addition to whether or not the diet has a high proportion of CHO:

(1) Isoenergetic conditions of feeding, i.e., when energy balance is in equilibrium. It has been reported in healthy subjects that on diets containing a very high proportion of CHO (75%) for 25 days, the fractional de novo hepatic lipogenesis increased [13]. However, the conversion of CHO into fat does not provide any net storage of fat to the body: the fat synthesized by de novo lipogenesis in tissues is balanced out by simultaneous fat oxidation in another tissue.
(2) Overfeeding conditions, i.e., in persisting positive energy balance. Based on a review of several published studies [33], one can conclude that, in hyperenergetic conditions, high prolonged carbohydrate overfeeding leads to a net gain in body fat due to two processes: (1) an enhanced de novo lipogenesis and (2) a decreased whole body fat oxidation (i.e., a sparing of endogenous fat) consecutive to the rise in CHO oxidation (Fig. 5). In parallel, triacyglycerol plasma concentrations increased [14] and if prolonged, deleterious effects are observed such as fatty liver and hepatic dysfunction [8].

However, since the net energetic efficiency of conversion of CHO to fat is much lower than the net efficiency of

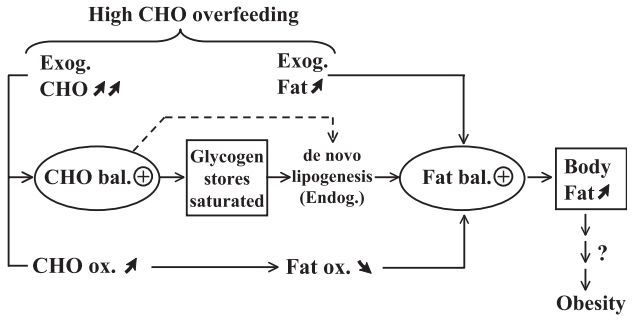

Fig. 5. General diagram showing how prolonged high-CHO–mixed diet overfeeding can lead to positive fat balance by a dual mechanism: the increased carbohydrate oxidation consecutive to excess CHO intake will inhibit fat oxidation (antilipolytic action of insulin) contributing to make fat balance positive. Subsequently, the continuous increase in carbohydrate balance will result in an increase in glycogen stores, which will become progressively saturated. Substantial rates of carbohydrate conversion into fat are induced only when the glycogen stores are first enlarged and CHO overfeeding is maintained (see Fig. 4).

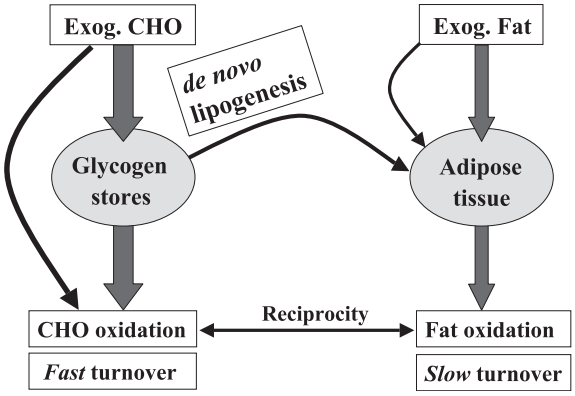

Fig. 6. This scheme shows that in certain nutritional circumstances (high, hyperenergetic carbohydrates diets), lipogenesis represents a sort of "carbohydrate sink" (i.e. a glycogen overflow pathway). As a result, the stimulation of de novo lipogenesis after a few days overfeeding (in particular with excessive carbohydrates) will increase body fat stores. This process is essential for achieving a new state of carbohydrate balance. In addition, note that a general reciprocity occurs in carbohydrates vs. fat utilization, the higher the former, the lower the latter.

storage of exogenous fat in adipose tissue, the excess energy storage will theoretically be lower with CHO as compared to fat overfeeding.

In conclusion, in conditions of energy balance, high-CHO low-fat diets do not result in a large stimulation of net de novo lipogenesis. On the contrary, such diets when prescribed ad libitum have shown to induce progressive slow weight losses (in the order of a few kilograms) in individuals of various body weight and BMIs [7,16,22], suggesting modest negative energy balance. As a result, the increase in lipidaemia generally observed with controlled high-CHO diets [14] may be offset by the weight loss resulting from the low spontaneous ad lib consumption of such diets.

Furthermore, low-fat–high-CHO diets may be particularly useful in preventing weight (re)gain rather than inducing substantial weight loss. Note that these high-CHO diets should be based on "normal" food (rich in vegetables and legumes), rather than in the form of high-sugar food items or high-sugar drinks.

In contrast, when persistent positive energy balance is induced by massive CHO overfeeding, net de novo lipogenesis is progressively activated and this process may become quantitatively important with time. A large positive imbalance in CHO intake (and hence CHO balance) will result in more de novo lipogenesis than a small positive imbalance. When saturation of glycogen stores occurs and there is a fixed level of energy expenditure (i.e., no additional exercise), the diversion of excess CHO into fat will be operating as virtual "sink" process (Fig. 6), necessary to dispose of the excessive exogenous CHO.

Note, however, that this massive hyperenergetic high-CHO diets are in most situations of natural life conditions extremely difficult to ingest for prolonged periods of time with "normal" foods, due to the higher satiating power of CHO as compared to fat [7]. It should be recalled that in overfeeding situations (including protein overfeeding), excess energy will be ultimately stored in the form of fat, irrespective of the nature of the surfeit macronutrients. There is no other form of long-term concentrated energy reserve.

The rate of de novo lipogenesis may be influenced not only by the absolute amount and duration of CHO feeding but also by the type of CHO ingested [21]. For example, food (or meals) with low glycemic index may be more favorable in moderating de novo lipogenesis since the pattern of CHO oxidation will be delayed as compared to food with high glycemic index and therefore large excursion in RQ in the postprandial phase is prevented, a time at which de novo lipogenesis is stimulated.

The real contribution of de novo lipogenesis in obesity development is largely unknown since this would require to partition the excess fat storage in the different types of obesity resulting from (a) exogenous dietary fat vs. (b) de novo fat synthesis. The fact that the pattern of fatty acid composition of the adipose tissue reflects the pattern of exogenous fatty acid [5] suggests that de novo lipogenesis from CHO may be a small contributor as compared to exogenous fat. In conclusion, de novo lipogenesis from carbohydrates does not substantially affect daily fat balance in usual conditions of nutrition.

Future investigations upon the molecular factors involved in the regulation of body fat balance (leptin, ghrelin, PYY, PPARγ, αMSH, NPY, etc.), which have not been mentioned here, will hopefully provide a better understanding of whether endogenous factors indeed play a crucial role in the development of excess body fat and ultimately obesity in humans.

References

[1] Aarsland A, Chinkes D, Wolfe RR. Hepatic and whole-body fat synthesis in humans during carbohydrate overfeeding. Am J Clin Nutr 1997;65:1774–82.
[2] Acheson KJ, Schutz Y, Bessard T, Flatt JP, Jéquier E. Carbohydrate metabolism and de novo lipogenesis in human obesity. Am J Clin Nutr 1987;45:78–85.
[3] Acheson KJ, Schutz Y, Bessard T, Ravussin E, Jéquier E, Flatt JP. Nutritional influences on lipogenesis and thermogenesis after a carbohydrate meal. Am J Physiol 1984;246:E62–70.
[4] Acheson KJ, Schutz Y, Bessard T, Anantharaman K, Flatt JP, Jequier E. Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. Am J Clin Nutr 1988;48(2):240–7.
[5] Beynen AC, Hermus RJ, Hautvast JG. A mathematical relationship between the fatty acid composition of the diet and that of the adipose tissue in man. Am J Clin Nutr 1980;33:81–5.
[6] Bjorntorp P, Sjostrom L. Carbohydrate storage in man: speculations and some quantitative considerations. Metabolism 1978;27(Suppl. 2):1853–65.
[7] Blundell JE, Stubbs RJ. High and low carbohydrate and fat intakes: limits imposed by appetite and palatability and their implications for energy balance. Eur J Clin Nutr 1999;53(Suppl. 1):S148–65.
[8] Chascione C, Elwyn DH, Davila M, Gil KM, Askanazi J, Kinney JM. Effect of carbohydrate intake on de novo lipogenesis in human adipose tissue. Am J Physiol 1987;253:E664–9.

[9] Flatt JP. Glycogen levels and obesity. Int J Obes 1996;20(Suppl. 2): S1–11.
[10] Flatt JP. Macronutrient composition and food selection. Obes Res 2001;9(Suppl. 4):256S–62S.
[11] Frayn KN, Whitley HA. Carbohydrate and fat balance: separate existences or an intimate relationship? Eur J Clin Nutr 1997;51:789.
[12] Hellerstein MK. De novo lipogenesis in humans: metabolic and regulatory aspects. Eur J Clin Nutr 1999;53(Suppl. 1):S63–5.
[13] Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. J Clin Invest 1996;97:2081–91.
[14] Jeppesen J, Schaaf P, Jones C, Zhou MY, Chen YD, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997; 65:1027–33.
[15] Kleiber M. Regulation of food intake. The fire of life, an introduction to animal energetics. Huntington (NY): Robert E. Krieger Publishing; 1961. p. 289.
[16] Lyon XH, Di Vetta V, Milon H, Jéquier E, Schutz Y. Compliance to dietary advice directed towards increasing the carbohydrate to fat ratio of the everyday diet. Int J Obes Relat Metab Disord 1995;19:260–9.
[17] Maffeis C, Armellini F, Tato L, Schutz Y. Fat oxidation and adiposity in prepubertal children: exogenous versus endogenous fat utilization. J Clin Endocrinol Metab 1999;84(2):654–8.
[18] Martinez JA, Fruhbeck G. Regulation of energy balance and adiposity: a model with new approaches. Rev Esp Fisiol 1996;52: 255–8.
[19] Minehira K, Bettschart V, Vidal H, Vega N, Di Vetta V, Rey V, et al. Effect of carbohydrate overfeeding on whole body and adipose tissue metabolism in humans. Obes Res 2003;11:1096–103.
[20] Nagy TR, Goran MI, Weinsier RL, Toth MJ, Schutz Y, Poehlman ET. Determinants of basal fat oxidation in healthy Caucasians. J Appl Physiol 1996;80(5):1743–8.
[21] Parks EJ. Changes in fat synthesis influenced by dietary macronutrient content. Proc Nutr Soc 2002;61:281–6.
[22] Raben A, Macdonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14 d ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. Int J Obes Relat Metab Disord 1997;21:846–59.
[23] Schrauwen P, van Marken Lichtenbelt WD, Saris WHM, Westerterp KR. Fat balance in obese subjects: role of glycogen stores. Am J Physiol 1998;274:E1027–33.
[24] Schutz Y, Acheson KJ, Jequier E. Twenty-four-hour energy expenditure and thermogenesis: response to progressive carbohydrate overfeeding in man. Int J Obes 1985;9(Suppl. 2):111–4.
[25] Schutz Y, Flatt JP, Jéquier E. Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity. Am J Clin Nutr 1989;50(2):307–14.
[26] Schutz Y, Tremblay A, Weinsier RL, Nelson KM. Role of fat oxidation in the long-term stabilization of body weight in obese women. Am J Clin Nutr 1992;55(3):670–4.
[27] Schutz Y. Abnormalities of fuel utilization as predisposing to the development of obesity in humans. Obes Res 1995;3(Suppl. 2): 173S–8S.
[28] Schutz Y. Does conversion of carbohydrate to fat contribute to obesity in humans ? Obes Matters 1999;2:18–22.
[29] Schutz Y. Macronutrients and energy balance in obesity. Metabolism 1995;44(9 Suppl. 3):7–11.
[30] Schutz Y. On problems of calculating energy expenditure and substrate utilization from respiratory exchange data. Z Ernähr Wiss 1997;36(4):255–62.
[31] Schutz Y. Role of substrate utilization and thermogenesis on bodyweight control with particular reference to alcohol. Proc Nutr Soc 2000;59(4):511–7 [Erratum in: Proc. Nutr. Soc. 2002; 61 (2): 319].
[32] Schutz Y. The adjustment of energy expenditure and oxidation to energy intake: the role of carbohydrate and fat balance. Int J Obes Relat Metab Disord 1993 (Dec);17(Suppl. 3):S23 [Discussion S41–S42].
[33] Shah M, Garg A. High fat and high-carbohydrate diets and energy balance. Diabetes Care 1996;19:1142–52.
[34] Weinsier RL, Bracco D, Schutz Y. Predicted effects of small decreases in energy expenditure on weight gain in adult women. Int J Obes Relat Metab Disord 1993;17(12):693–700 [Dec.].