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PAPER

Concept of fat balance in human obesity revisited with particular reference to *de novo* lipogenesis

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The measurement of fat balance (fat input minus fat output) involves the accurate estimation of both metabolizable fat intake and total fat oxidation. This is possible mostly under laboratory conditions and not yet in free-living conditions. In the latter situation, net fat retention/mobilization can be estimated based on precise and accurate sequential body composition measurements. In case of positive balance, lipids stored in adipose tissue can originate from dietary (exogenous) lipids or from nonlipid precursors, mainly from carbohydrates (CHOs) but also from ethanol, through a process known as *de novo* lipogenesis (DNL). Basic equations are provided in this review to facilitate the interpretation of the different subcomponents of fat balance (endogenous *vs* exogenous) under different nutritional circumstances. One difficulty is methodological: total DNL is difficult to measure quantitatively in man; for example, indirect calorimetry only tracks net DNL, not total DNL. Although the numerous factors (mostly exogenous) influencing DNL have been studied, in particular the effect of CHO overfeeding, there is little information on the rate of DNL in habitual conditions of life, that is, large day-to-day fluctuations of CHO intakes, different types of CHO ingested with different glycemic indexes, alcohol combined with excess CHO intakes, etc. Three issues, which are still controversial today, will be addressed: (1) Is the increase of fat mass induced by CHO overfeeding explained by DNL only, or by decreased endogenous fat oxidation, or both? (2) Is DNL different in overweight and obese individuals as compared to their lean counterparts? (3) Does DNL occur both in the liver and in *adipose tissue*? Recent studies have demonstrated that acute CHO overfeeding influences adipose tissue lipogenic gene expression and that CHO may stimulate DNL in skeletal muscles, at least *in vitro*. The role of DNL and its importance in health and disease remain to be further clarified, in particular the putative effect of DNL on the control of energy intake and energy expenditure, as well as the occurrence of DNL in other tissues (such as in myocytes) in addition to hepatocytes and adipocytes.

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Introduction

The measurement of fat balance (fat input minus fat output) involves the accurate estimation of both metabolizable fat intake and total fat oxidation.

Fat balance in man can be assessed in the postprandial phase (typically 3–5 h): this represents an 'apparent' fat balance since not all the exogenous fat is absorbed during this short period. This permits one to track, for example, interprandial retention of substrates or to identify the nature of mobilization of substrates (eg carbohydrate (CHO) *vs* fat), for example, in response to muscular activity. The duration over which fat balance is assessed is important. In typical nutritional studies, fat balance is evaluated over 24 h (or more) using a respiration chamber to continuously measure energy expenditure and substrate oxidation.[1–4] Fat balance is closely linked to energy balance when considered over weeks and months. This means that continuous positive energy balance is essential to gain fat. Measurement of fat balance is possible mostly under laboratory conditions and not easily performed in free-living conditions. However, net fat retention of mobilization—if of sufficient magnitude (more than about 2 kg)—can be estimated from accurate sequential body composition measurements (see further).

In positive balance, lipids stored in adipose tissue can originate from dietary (exogenous) lipids or from nonlipid precursors, mainly from CHOs but also from ethanol, that is, from substrates, which produce acetyl-CoA (during their catabolism), and are therefore susceptible to be converted to fatty acids in the intermediary metabolism. This process is known as *de novo* lipogenesis (DNL). Only the process of DNL from CHO will be discussed here.

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What is the real quantitative importance of DNL in man? More than 25 y ago, the late Bjorntörp *et al*[5] pointed out that, even with high isocaloric CHO meals, DNL was a quantitatively minor process in obese and nonobese individuals maintaining body weight.

The assertion as to whether DNL is a limited process in man (or not) depends upon the judgment of the investigators and the comparison to which the magnitude of this process is made (CHO utilization *vs* fat storage accounted for by DNL). The way of expression of DNL (absolute *vs* relative terms) is also important for the latter judgement and also remains an issue.

The conversion of CHO into fat is a high energy-requiring process as compared to the direct storage of exogenous fat as body fat. About 25% of the energy content of CHOs is converted into heat, whereas the deposition of dietary triglycerides into adipose tissue requires only about 2% energy. Therefore, DNL from CHO would theoretically constitute a protective factor inhibiting the increase in body fat stores. Acheson and Flatt[6] have claimed that the net energy cost of DNL due to substrate handling is hardly greater than the cost of direct oxidation of an equivalent amount of CHO not transformed into fat. The logical question related to this issue is how the direct energy 'cost of oxidation' of a substrate—a process that aims at providing ATP's rather than consuming it—could be greater than the cost of transformation of the same substrate into another substrate. Another issue which contradicts Acheson's assumption is that the magnitude of overall DNL (estimated by indirect calorimetry) has been found to be positively and highly significantly correlated ($r = 0.71$) to the thermic effect of food in a situation in which there is no net fat storage due to DNL over 24 h.[7] The slope of the regression line suggests that a net lipogenesis of 10 g/day increases the absolute thermogenesis by 70%.

The purpose of this article is to review the concept of fat balance and to explore to what extent DNL in particular from CHOs affects daily fat balance and hence may contribute to the development of obesity. How is fat balance defined?

Operational definition of fat balances

Fat balance (fat in minus fat out) is a simple but important concept, which is often disregarded in obesity development: the conditions of static *vs* dynamic fat balance are important to emphasize (Figure 1). A refinement of its definition by taking into account its qualitative components permits to better understand the various origin of fat storage (exogenous fat *vs* DNL in case of surfeit CHO).

Here, for the purpose of simplicity, fat oxidation in the fat balance equation will be considered separately from CHO oxidation, but one should realize that both are not mutually independent and that there is an intimate interrelationship between them. Indeed, in isoenergetic conditions, at a fixed energy expenditure level and keeping protein intake essentially constant, there is an inverse relationship between CHO and fat oxidation—the greater the proportion of CHO oxidation, the lower the proportion of fat oxidation. This appears to be essential for our understanding of the effect of increased CHO intake on the sparing of endogenous fat through a blunting of fat oxidation.

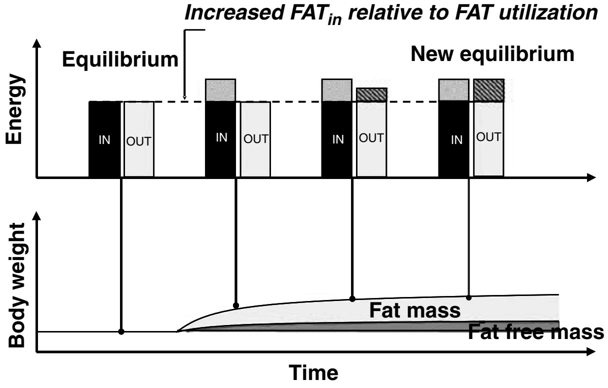

Figure 1 Static phase *vs* dynamic phase in fat balance. Note the slow re-equilibration of fat balance following a step increase in exogenous fat. The time required to reach a new equilibrium in fat balance is very long (years)—everything kept constant—and depends upon the extent to which fat oxidation rises consecutive to the increased adipose tissue.

The fat balance equation can be defined in *static* or *dynamic* conditions.

STATIC fat balance:

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

Negative balance leads to body fat loss. Positive fat balance leads to body fat gain. Obesity can only result from a chronic state of positive fat balance.

Obesity develops during a *dynamic phase* during which fat balance remains positive for a prolonged period of time (Figure 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 net effect, that is, positive fat balance not subsequently corrected by negative ones.

In the *dynamic* phase of weight gain, change (Δ) in fat balance can be calculated as

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

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.

A new equilibrium is eventually reached after several months, or years, depending upon several factors. These include initial fat (energy) balance imbalance as well as initial body fat, the more excess fat in the body, the more time it will take to reach equilibrium and the more body fat will be gained.

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

$$\begin{aligned}\text{Fat balance} = {} & (\text{Exogenous fat intake} \\ & + \text{endogenous fat synthesis}) \\ & - (\text{exogenous} \\ & + \text{endogenous fat oxidation})\end{aligned} \tag{3}$$

Exogenous fat oxidation corresponds to the proportion of total fat oxidation accounted for by exogenous sources (ie fat in the diet).

This is assessed by using exogenous fatty acids labeled with C13 and integrated in the meal, and by measuring the C13 abundance in the expired air.[8–10] Since exogenous fat in the postprandial phase is mostly stored (in adipose tissue), the fraction oxidized is generally low, ranging from 10 to 20% of the exogenous fat intake, depending upon the conditions of measurements (duration) as well as the composition of the diet.

Endogenous fat synthesis corresponds to the process of DNL from CHO. If we ingest massive hyperenergetic loads of CHO *without exogenous fat*, the fat balance equation simplifies to

$$\begin{aligned}\text{Fat balance} = {} & \text{Endogenous fat synthesis} \\ & - \text{Endogenous fat oxidation}\end{aligned} \tag{4}$$

This is because exogenous fat intake and exogenous fat oxidation are both zero.

Note that this 'endogenous' fat balance precisely corresponds to net DNL assessed by indirect calorimetry. When both sides of the equation are identical, there is no net DNL and the (nonprotein) RQ is equal to 1.0 (see further). 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 without exogenous fat. This signifies that DNL can occur without being tracked by indirect calorimetry, since it is offset by simultaneous oxidation of a similar amount of fat in other tissues. A brief description of the methods available to assess DNL is given here.

How is DNL estimated?

Technically, measuring whole-body total DNL in man is difficult. The techniques that have been developed to assess DNL include indirect calorimetry, tracer studies (stable nonradioactive isotopes such as heavy carbon C13 or heavy water deuterium D2), as well as many more indirect estimates based on changes in body composition in conjunction with the sequential assessment of whole-body nutritional balances.

The Guru Walla natural overfeeding tradition in Cameroon[11] is of interest to demonstrate the way DNL can be tracked from changes in body composition and precise daily food intake assessment. The adolescents ingested more than 7000 kcal CHO per day and gained 12 kg body fat over 10 weeks. Since over this period they ingested a total of 4 kg fat as food, this suggests that as much as 8 kg fat (ie 12 minus 4) was synthesized *de novo* from CHO, that is, an average of 114 g net fat synthesis per day. This is undoubtedly an underestimation since it assumes that exogenous fat has been stored with 100% efficiency. The duration of the experiment as well as the huge CHO excess-generating substantial DNL-allowed the utilization of this indirect approach involving no indirect calorimetric measurement to assess overall DNL.

Indirect calorimetry measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2). 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 ($RQ = VCO_2/VO_2$) surpasses the value of $1.0 = RQ$ of CHOs. This is because RQ of the transformation of CHO into fat is very high (2.75 for palmitate). It should be stressed that pulmonary hyperventilation of the subject, which increases RQ, should be excluded.

One issue rarely considered in the interpretation of indirect calorimetry data is that DNL induced by massive ingestion of CHO under maintenance conditions is mostly a 'transitory state', as evidenced from the profile of RQ (Figure 2). Indeed, the net lipogenesis generally occurs over a short period of time (during which fat synthesis surpasses fat oxidation), as evidenced by the duration during which RQ goes beyond 1.0. If the RQ assessment by indirect calorimetry is made continuously minute by minute over a long period, this will be easily tracked. However, if the calorimetric measurement is averaged for over an hour or so, DNL may be missed since the transitory peak RQ value above one is 'hidden' in the average RQ; the latter may remain close to or below 1.0 (Figure 2).

In the late 20th century, a novel isotopic method called 'mass isotopomer distribution analysis' (MIDA) had been developed by Hellerstein's group[11–13] to assess hepatic DNL,

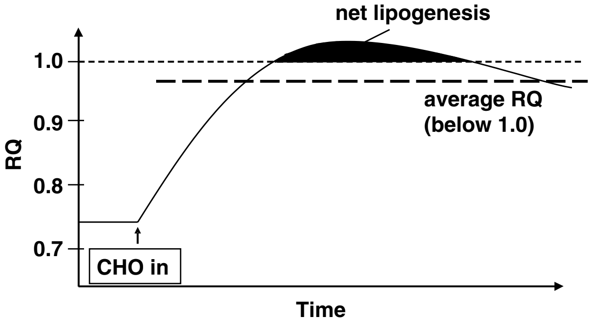

Figure 2 Theoretical time course of respiratory quotient in response to acute CHO overfeeding. Indirect calorimetry only estimates net lipogenesis in a transitory phase during which the respiratory quotient is greater than 1.0, that is, when *de novo* fat synthesis by the lipogenesis process surpasses fat oxidation (see equation (4) in the text).

based on monitoring the rate of incorporation of [^{13}C]acetate into VLDL-palmitate synthesis. Hepatic DNL is measured by mass isotopomer distribution analysis from [^{13}C]acetate infusions. An alternative tracer method described recently is based on an estimate of the fractional biosynthetic rate from the incorporation of deuterated water (D_2O) derived from total plasma water pool into triglycerides in blood or adipose tissue fatty acids.

It should, however, be borne in mind that, in order to quantitatively evaluate adipose tissue DNL, the incorporation of label in adipose tissue during short-term administration of labeled precursors is generally too short, due to the slow turnover of adipose tissue triglycerides. Therefore, monitoring tracer incorporation into adipose tissue lipids might be impractical due to the huge dilution of the tracer in the large adipose triglyceride pool.

It should also be pointed out that the different techniques measure different things: indirect calorimetry assesses lipogenesis at the whole-body level but only *net* (not total) lipogenesis. In contrast, MIDA measures the rate of lipogenesis in one organ only (the liver) and adipose tissue DNL is excluded in the measurement. Obviously, the combination of both techniques appears to be very useful.[14] When overall fat balance is used as a method, excess endogenous fat storage assesses the product of DNL being stored in all tissues.[15,16]

Effect of energy balance on DNL induced by CHOs

Two nutritional conditions should be envisaged, since they have different effects on the magnitude of DNL:

(1) *Isoenergetic* conditions of feeding, that is, when there is energy balance in equilibrium: Fractional *de novo* hepatic lipogenesis increases since part of the exogenous CHO is channelled into fat. However, the conversion of CHO into fat does not provide any net storage of fat to the body: the fat synthesized by DNL in tissues is balanced out by simultaneous fat oxidation in another tissue (see Eq. 4).

(2) *Overfeeding* conditions (positive energy balance): Prolonged high CHO overfeeding leads to a net gain in body fat due to several processes working in the same direction:[15–17]

(a) an enhanced DNL (Figure 3), (b) a substantial decrease in whole-body fat oxidation, that is, a sparing of endogenous fat utilization and (c) the efficient storage of exogenous fat ingested in conjunction with CHOs. The three processes contributing to increase fat storage during high CHO overfeeding are depicted in Figure 4. Note that triacylglycerol plasma concentrations increased and, if CHO overfeeding

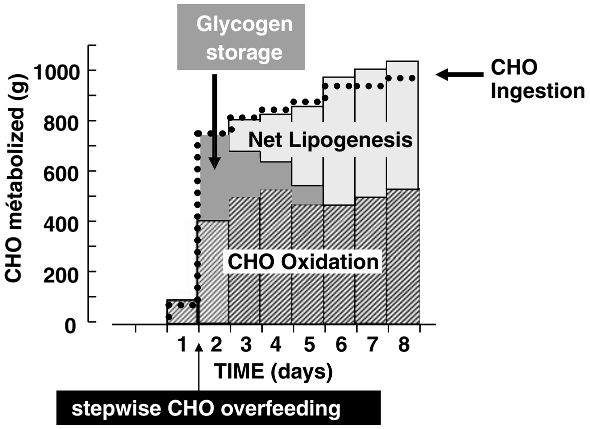

Figure 3 Progressive CHO overfeeding over 1 week—in conditions difficult to apply in real life—engenders a dramatic increase in DNL (see Schutz *et al*[15,16]). After a few days, CHO oxidation 'plateaus' being limited by the rate of total energy expenditure. The excess exogenous CHO is chanelled to fat once the glycogen stores have been filled up. Prolonged high-intensity exercise constitutes a physiological phenomenon susceptible to cut down DNL acutely by drastically increasing endogenous CHO oxidation in muscles.

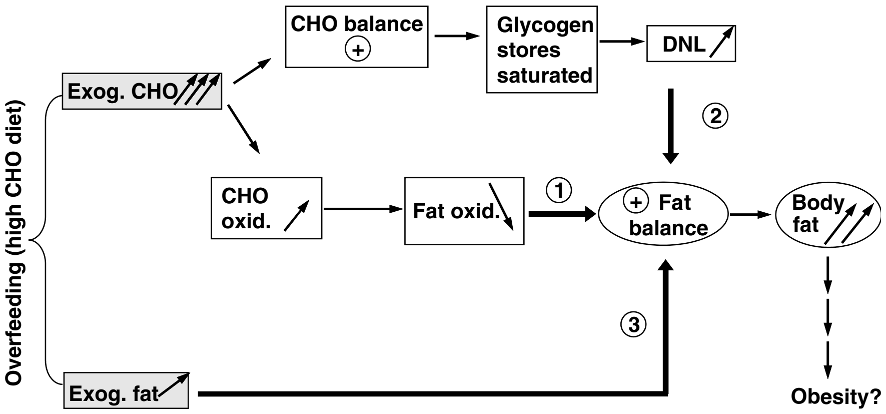

Figure 4 General diagram showing how prolonged high CHO-mixed diet overfeeding can lead to substantial positive fat balance by the three mechanisms outlined.

is prolonged, deleterious effects are observed, such as fatty liver and hepatic dysfunction.[18]

The net energetic efficiency of conversion of CHO to fat is much lower than the net efficiency of storage of exogenous fat in adipose tissue. As a result, calorie per calorie, the theoretical excess energy storage will be lower with CHO overfeeding as compared to fat overfeeding.[19]

When saturation of glycogen stores occurs the diversion of excess CHO into fat will be operating as a virtual ‘sink’ process or a sort of safety valve.[12] It is necessary to dispose of the excessive exogenous CHO, since this is limited by the magnitude of the oxidation process in the tissues consuming glucose.

Taken together, the process of DNL may reveal its importance in the regulation of CHO disposal: an elevated insulin level (mediated through excess CHO ingestion) leads to an increased DNL in the liver. This phenomenon may reveal its importance, since it contributes to preventing a state of hyperglycemia by diverting excess glucose into fat and contributing in assuring a more appropriate control of glycemia. Incidentally, it should be kept in mind that the increased *de novo* triglyceride synthesis disrupts fat metabolism and may exacerbate insulin resistance to an extent, which remains to be investigated.

The rate of DNL may be influenced not only by the absolute amount and duration of CHO feeding but also by the type of CHO ingested, although a recent study failed to observe a difference between sucrose and glucose ingestion.[20] For example, it can be assumed that food (or meals) with low glycemic index may be more favorable in moderating DNL since the pattern of CHO oxidation and storage will be delayed as compared to food with high glycemic index.[21] As a result, a large positive excursion is prevented in respiratory quotient in the postprandial phase, a time at which DNL is stimulated.

In conclusion, DNL from CHOs affects fat balance when surfeit CHO is ingested over a sufficient period of time in conditions of positive energy balance. However, it does not affect the daily fat balance in usual isoenergetic conditions when mixed meals are ingested and body weight is maintained.

Weight gain with high CHO diets and effect of DNL

An important issue is the hypothesis that the increased fat mass observed in the dynamic phase of obesity development is secondary to excess fat deposition via the activation of DNL.

First, the issue of whether excess CHO is a risk factor for weight gain via the stimulation of DNL remains controversial. CHO as such has been classically considered as ‘making you fat’ without considering the fact that rapid weight gain with high CHO diets is initially due to increased glycogen stored with associated water, rather than due to fat storage (Figure 5).

Several arguments could be in favor of excess CHO being a risk factor for body weight gain, in particular, ‘passive CHO overconsumption’, similar to that observed with fat, but with a major difference, because CHO is taken in liquid form.[22]

The arguments that have been put forward to refute CHO as a risk factor for weight gain are as follows: (a) solid evidence of DNL in adipose tissue is still lacking (see further), (b) the energetic efficiency of DNL is low due to the high energy cost of this process, (c) DNL is judged by certain investigators as not very active and not quantitatively important even with high CHO diets, (d) exogenous CHO is mostly oxidized postprandially and an increased CHO

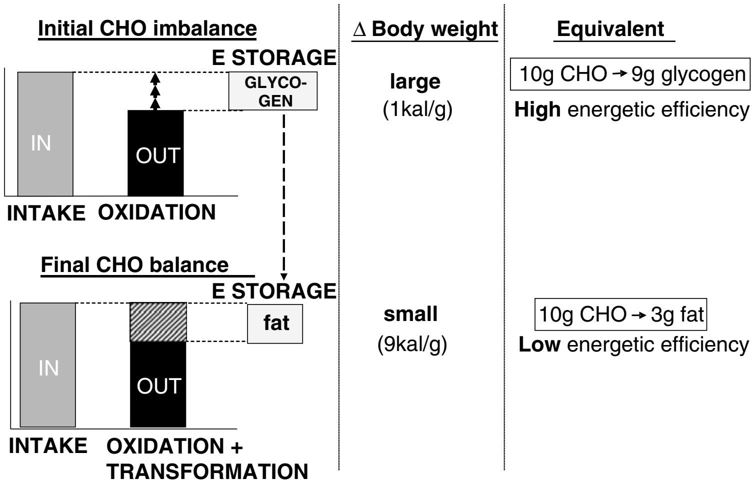

Figure 5 Prolonged CHO overfeeding—through its effect on insulin—leads to an expansion of the glycogen stores, which will become saturated. During this time, body weight will substantially increase (low energy density of the glycogen–water pool). Substantial rates of CHO conversion into fat (ie DNL) are induced only when the glycogen stores are saturated. Body weight gain during lipogenesis is minimized because of the low energetic efficiency of converting glucose into fat and the high energy density of fat storage.

intake results in an immediate rise in CHO utilization, and hence there is little left for DNL.

We have to recall that if high-CHO meals promote CHO oxidation and storage, this is not the case after high-fat meals, which mainly consist in a stimulation of exogenous fat storage without effective stimulation of fat oxidation.[23] The increase in fat mass is accompanied by an enhanced rate of FFA release into the circulation, which contributes to stimulate fat oxidation. This is not an acute process as with CHO.

The effect of CHO overfeeding on the disposal of a large oral glucose load has been the object of classical studies in our Institute,[15,23–25] but has been recently reinvestigated (using indirect calorimetry) by modern technology.[26] We found that, under standard isoenergetic conditions, less than half of the exogenous glucose was oxidized in the postprandial phase (5 h). The remaining was stored as glycogen and very little net DNL occurred (less than 5% of the glucose load).

The issue of what level of CHO intake is critical for inducing net DNL remains open. According to Hellerstein,[27] DNL becomes a quantitatively major pathway under one condition: when total CHO intake—expressed in energy terms—exceeds total energy expenditure, that is, when more than 100% of the energy requirement is covered by CHO ingestion. He rightly pointed out that this circumstance is unusual in daily life.

As mentioned previously, there are other factors of importance: both the total quantity of CHO ingested and the proportion of CHO expressed as total food energy (%CHO energy), in addition to the status and characteristics of the host such as the size of the glycogen stores. Let us consider a maintenance mixed diet containing 55% CHO energy fed for several weeks. Supposing that the food intake doubled on multiplying the total quantity of CHO by two: since total CHO energy will be greater than total energy expenditure (state of positive energy balance), according to Hellerstein,[27] DNL will become important in this situation. However, based on the concept of food quotient (FQ) developed by Flatt,[28] the FQ will remain identical in both situations at a value in the order of 0.85 (mixed diet). In fact, we do not anticipate much net lipogenesis—as measured by indirect calorimetry—during mixed diet overfeeding.[29] The reason is that the amplitude of the rise in RQ in response to overfeeding (RQ will be greater than FQ in positive energy balance) will remain below 1.0. Indeed, we can anticipate that the absolute amount of CHO oxidized will progressively increase and hence fat oxidation will be depressed. This is a situation where 'hidden' DNL may occur after the size of the glycogen stores has increased without substantial apparent net DNL.

Do obese women convert more CHO to fat than lean women?

The regulation of whole-body and adipose tissue DNL in overweight subjects has not been extensively investigated. The level of hepatic DNL in the obese has been found to be either unchanged[26,30] or increased.[31] The major confounding factor seems to be the degree of insulin resistance.[32]

The key issue is whether or not obesity (at least some form of obesity) may be associated to an increase in DNL through the regular consumption of high CHO meals in state of positive energy balance.

McDevitt *et al*[20] investigated DNL in lean and obese women in response to both a control isoenergetic diet and an energy excess due to CHO overfeeding. The test diets were CHO enriched with either sucrose or glucose, providing enough energy to maintain energy balance or to provide energy at 50% in excess of daily energy requirements. The type of CHO overfeeding (sucrose *vs* glucose) showed no significant difference in DNL. With the control diet, DNL was nearly twice the rate in the obese than in the lean subjects, regardless of the source of the CHO. The absolute value of DNL in this study can be judged as low. Technical factors are unlikely to explain the low rates of DNL reported by McDevitt *et al*,[20] since their method may overestimate DNL because the deuterium method, if anything, will result in an artifactual overestimation of a few percent of DNL, and elongation of fatty acids might add a further slight overestimation of DNL.

In our laboratory, the effect of acute CHO overfeeding on whole-body DNL and adipose tissue lipogenic gene expression has recently been studied in lean and overweight subjects.[26] Whole-body net DNL increased after ingestion of a single large CHO meal confirming previous studies. Surprisingly, DNL was lower in the obese as compared to their lean counterparts. The difference was on the borderline of statistical significance. In a more recent overfeeding study also performed in overweight subjects, whole-body net DNL was found to be lower than in normal subjects (Figure 6).[33]

One explanation for the lower value in overweight subjects is that their impaired suppression of plasma-free fatty acids observed after CHO loading may contribute to blunt net DNL, since it seems that fatty acids inhibit the expression of lipogenic enzymes.[33]

This study concluded that whole-body net DNL is not increased in overweight individuals in the situation of positive energy balance induced by CHO overfeeding.

Indeed, it should be recalled that stimulation of adipose tissue lipogenic enzymes was not higher in overweight subjects after CHO overfeeding; the mRNA levels of adipose tissue transcription factor sterol regulatory element binding protein-1c (SREBP-1c), which regulates the expression of lipogenic enzymes, increasing less in overweight (by 25% as an average) as compared to lean subjects (43% increase), but the difference was statistically nonsignificant. Fatty acid synthase (FAS) mRNA increased by 66 and 84%, respectively, corroborating the lipogenic role of adipose tissue.[14]

In summary, in our study, CHO overfeeding did not stimulate to a larger extent whole-body net DNL or expression of lipogenic enzymes in adipose tissue of overweight subjects as compared to their lean counterparts.

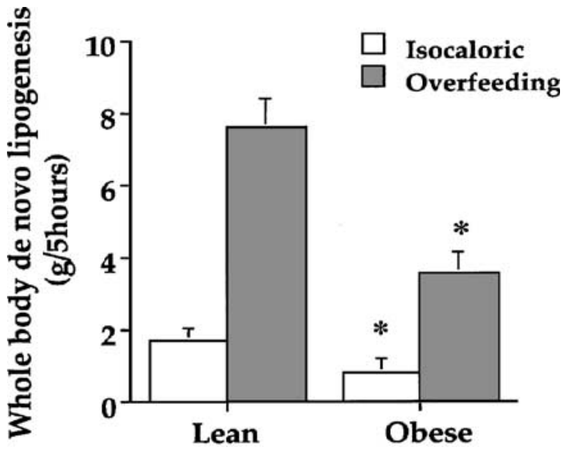

Figure 6 DNL during isoenergetic feeding or during acute CHO overfeeding in lean and obese subjects.[33]

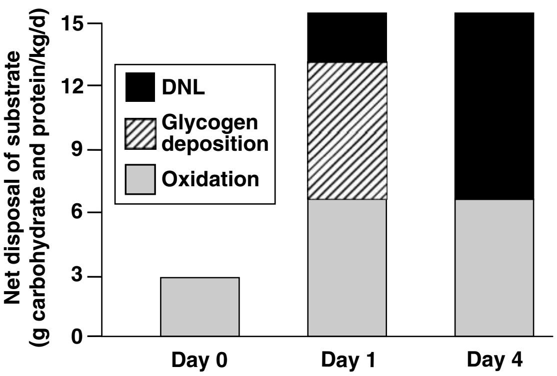

Figure 7 By combining indirect calorimetric and stable isotopic techniques, Aarsland *et al*[14] were able to make the hypothesis that DNL must occur in adipose tissue. Note the magnitude of DNL after 4 days of CHO hyperalimentation.

Another CHO overfeeding study performed in lean and obese women confined into a calorimetric chamber[34] found no net DNL in either group of subjects when estimated over 24 h even though excess CHO intake surpassed their maintenance energy requirements by 50%.

Is DNL a strictly hepatic process? Does fat synthesis from CHOs occur in adipose tissue?

Under *in vitro* conditions, adipose tissue has been shown to synthesize lipids *de novo*.[5] However, clear evidence that DNL is more active in adipose tissue obtained from obese than lean subjects is lacking.

The site of DNL is classically thought to be mostly the liver. In fact, the exact sites of fatty acid synthesis have not been 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. An important issue is what is the contribution of nonhepatic organs (adipose tissue and others) in the total DNL

Lipogenesis and the regulation of one of its core enzymes, FAS, in human adipose tissue in response to hormonal and nutritional manipulation has been studied.[35] The authors demonstrated that the lipogenesis that occurs in human adipose tissue can be induced by insulin, and further enhanced by glucocorticoids.

In a now classical study, Aarsland *et al*[14] simultaneously monitored whole-body net DNL with indirect calorimetry and hepatic net DNL by incorporation of [^{13}C]acetate into VLDL-triglyceride following several days of i.v. CHO hyperalimentation (Figure 7). These authors reported that whole-body net DNL—assessed by indirect calorimetry—far exceeded hepatic lipogenesis. The unexplained part, assumed to be adipose tissue DNL, could constitute a major site of lipogenesis under such conditions.

Under *in vivo* conditions, the quantitative importance of DNL in adipose tissue remains more questionable. This is due to the methodological limitations for measuring DNL in adipose tissue.

Guo *et al*[36] studied lean and obese individuals during uncontrolled energy intake, and reported that adipose tissue DNL, monitored by means of the incorporation of deuterated water into fatty acids, was very low. Similarly, Diraison *et al*[31] reported that healthy subjects fed an isoenergetic or hyperenergetic diet had very little adipose DNL, evaluated from incorporation of either [^{13}C]acetate or deuterated water into adipose tissue fatty acids, a different technique, as previously mentioned.

Nonetheless, the evidence that adipose tissue is a site of DNL may be derived from different observations:

(1) Increased mRNA expression of several lipogenic enzymes occurs after CHO overfeeding. The expression of SREBP-1c and FAS increases in adipose tissue of overfed lean humans.
(2) Increased fractional activity of the pentose-phosphate shunt pathway—providing reduced NADPH for fat biosynthesis—constitutes an indirect indicator of DNL.

Note that in the study described above,[33] the fractional activity of the pentose-phosphate pathway failed to increase after CHO overfeeding.

In conclusion, recent data indicate that whole-body net DNL is stimulated after acute CHO overfeeding in both lean and overweight individuals. SREBP-1c and FAS gene expressions suggest that adipose tissue is actively involved in CHO-induced DNL. Furthermore, there is some indication that the human muscle may constitute another possible site for DNL.[37]

Today, the effect of obesity on the magnitude of DNL is not clear since it may depend upon several factors related to this heterogenous condition such as hyperinsulinemia and insulin resistance, which may influence the expression of lipogenic markers. The medical and nutritional conditions and the metabolic disturbance occurring in the host may play a role in the magnitude of the DNL process.

Our understanding of DNL may still be in its infancy. DNL is functionally important and reflects an adapted state of the organism to deal with particular nutritional conditions to which it was not previously exposed. Its role in health and disease remains to be determined. Some individuals may have an intrinsically higher or lower DNL, perhaps constitutive and possibly of genetic origin.

Despite its potential importance in obesity and related disorders, little is known about regulation of DNL in human adipose tissue at the molecular and mechanistic levels.

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