Time Course of Increased Lipid and Decreased Glucose Oxidation During Early Phase of Childhood Obesity

CATHERINE LE STUNFF AND PIERRE-FRANÇOIS BOUGNÈRES

To determine the time course of metabolic dysfunctions in recent active obesity, we studied basal energy expenditure and lipid and glucose oxidation in 31 obese children (duration of obesity 1–11.5 yr), compared with 14 lean age-matched control subjects. Using indirect calorimetry in basal overnight fasting conditions, we found that obese children produced 15% more energy than control subjects. Obese children oxidized twice as much lipid (56 ± 4 mg/min) as normal children (25 ± 5 mg/min, $P < 0.0005$), so that lipid oxidation provided 61 ± 6% of overall energy production (vs. 33 ± 3% in control subjects, $P < 0.0005$). This increase of lipid oxidation was already present in the earlier stages of obesity. Glucose oxidation was diminished in the obese (93 ± 6 mg/min) compared with the control children (136 ± 6 mg/min, $P < 0.0005$) and accounted for only 39 ± 3% of energy production (67 ± 6% in control subjects, $P < 0.0005$). This decrease was not present initially and appeared after ~4 yr and worsened with obesity duration ($r = 0.72$, $P < 0.0005$). The results were similar when lipid and glucose oxidation were normalized to body surface area or lean body mass. We hypothesize that increased lipid oxidation is one of the earlier dysfunctions observed in recent-onset obesity and that lipid oxidation may induce a progressive decrease of glucose oxidation, insulin resistance, and increased fasting insulin secretion. *Diabetes* 42:1010–16, 1993

From the Hôpital Saint Vincent de Paul, Paris, France.

Address correspondence and reprint requests to Dr. Pierre Bougnères, Unité 342 INSERM, Hôpital Saint Vincent de Paul, 82 Avenue Denfert-Rochereau, Paris, France.

Received for publication 18 August 1992 and accepted in revised form 10 February 1993.

NIDDM, non-insulin-dependent diabetes mellitus; FPG, fasting plasma glucose; IBW, ideal body weight; OGTT, oral glucose tolerance test; FFA, free fatty acid; CV, coefficient of variation; RQ, respiratory quotient; NPRQ, nonprotein respiratory quotient; $\dot{V}o_2$, O_2 consumption; $\dot{V}co_2$, CO_2 production; LBM, lean body mass; RIA, radioimmunoassay; CoA, coenzyme A; EPR, energy production rate; BSA, body surface area.

Human obesity is associated with various degrees of impaired glucose homeostasis, ranging from glucose intolerance to NIDDM (1–3). These abnormalities reflect a dysregulation of the glucose fluxes entering the different metabolic pathways. In obese subjects with impaired glucose tolerance and marked hyperinsulinemia, the basal rate of glucose oxidation is normal, but after a glucose load, glucose oxidation is decreased by 50%, resulting in elevated plasma glucose levels, whereas glucose storage is normal (4). In contrast, obese patients with overt diabetes and hyperinsulinemia oxidize glucose normally both in the postabsorptive state and after glucose ingestion but show a severe decrease in the amount of glucose they can store after a glucose load (4).

These studies, performed in adult long-term obese patients, were important in understanding diabetes associated with obesity but do not give us any information about the initial metabolic events at the time of excessive growth of adipose tissue (5). Moreover, patients with long-term obesity could have developed compensatory mechanisms to overcome initial defects, making it difficult to recognize causal abnormalities.

This investigation was undertaken after the recent onset of obesity and describes early changes in resting metabolic rates and in the oxidation rates of carbohydrates and lipids. For this study, we selected children whose body-weight curve had been followed yearly since birth and who were gaining weight at the time of the experiments. At this phase of the obesity syndrome, FPG, glucose tolerance to an oral load, and fasting plasma insulin are still normal, which avoids potential interfering influences of hyperinsulinism and hyperglycemia.

We found that basal energy expenditure was increased versus age-matched lean subjects and that obese children were oxidizing more fat and less glucose. These changes progressed linearly during the first 12 yr

TABLE 1
Clinical characteristics of studied normal and obese children

	Normal children	Obese children	*P* value
n	14	31	
Sex (M/F)	7/7	16/15	
Age (yr)	11.9 ± 0.7	11.9 ± 0.4	NS
Body weight (kg)	39.5 ± 3.0	64 ± 3	<0.0005
IBW (%)	98 ± 0.1	160 ± 4	<0.0005
LBM (kg)	30 ± 3	35 ± 2	NS
Fat mass (kg)	9.5 ± 0.5	29 ± 1	<0.0005
Duration of obesity (yr)	—	6.1 ± 0.5	
Weight gain (kg last yr)	3.6 ± 0.2	9.1 ± 0.7	<0.0005
Plasma glucose (mM)	4.3 ± 0.1	4.3 ± 0.1	NS
Plasma FFA (mM)	0.83 ± 0.08	0.58 ± 0.09	<0.005
Plasma insulin (pM)	54 ± 4	64 ± 5	NS

Data are means ± SE.

of obesity. Only the increase in lipid oxidation was present in the earlier observations, suggesting that lipid oxidation could have a primary role among the metabolic changes associated with the constitution of obesity.

RESEARCH DESIGN AND METHODS

Patient population. We recruited 31 obese children, 7–16.5 yr of age (mean 11.9 ± 0.4 yr), with weights ranging from 127 to 209% of IBW (average 160 ± 4%). None of the children had any chronic disease or had family members with endocrine disorders or diabetes. All were in good health and had never attempted to reduce their caloric intake or experienced any weight loss since the onset of obesity 1.0–11.5 yr previously. The onset of obesity was dated when the subjects exceeded 120% of IBW for age (6). Thereafter, the children gained weight at various rates. The year preceding the study, weight increase averaged 9.1 ± 0.7 kg, two- to threefold the normal rate.

All children were hyperphagic, with an alleged caloric consumption of 4030 ± 156 kcal/day in girls and 4180 ± 210 kcal/day in boys. Plasma glucose was normal after 12 h of fasting (Table 1). At 120 min of OGTT, plasma glucose ranged from 4.0 to 6.4 mM, averaging 5.4 ± 0.1 mM; all obese children therefore had normal glucose tolerance according to the pediatric criteria of the National Diabetes Data Group (7).

For comparison, we studied 14 lean normal children, recruited from the families of investigators, colleagues, friends, and nurses, 11.9 ± 0.7 yr of age with weights ranging from 91 to 99% of IBW.

The investigative nature of our experiments was explained to the children and their parents before they gave their consent for the study, which was approved by the Institut National de la Santé et de la Recherche Médicale National Committee on Medical Bioethics.

Clinical characteristics of the obese and control children are presented in Table 1.

Procedural methods. During the 3 days before the test, obese and normal children were fed a normal diet, adjusted for age of the children (8), with respect to both caloric content (~1200 plus 100 kcal per year of age) and carbohydrate (50%) proportion (9). The obese children had their diet checked at the hospital, and the parents of the normal children received a detailed meal plan from the dietitian. The obese children did not lose weight during this prestudy period, and therefore none was considered in a catabolic state. The prestudy in the hospital was also used to train the young patients with the indirect calorimetry device.

FPG, FFA, and insulin were measured at 0730 after a 12-h fast. One hour later, continuous indirect calorimetry was performed using a Deltatrac Metabolic Monitor (Datex, Finland). During the 1-h experiment, the children rested comfortably on a bed and watched television or read. Urine was collected over the corresponding 24 h for measurement of urinary nitrogen. The intraexperiment CV (means ± SD) of RQ, $\dot{V}o_2$, and $\dot{V}co_2$ was determined to be 3–5% for each child.

The reproducibility of indirect calorimetry measurements was tested by repeating experiments in seven obese and three normal children. Mean relative individual CV was 3% for the determination of NPRQ and 14% for the determination of the rates of glucose and lipid oxidation.

Fat mass was determined using an equation based on multiple skin-fold measurements, as reported previously (10–12). From this evaluation of fatness, LBM was approximated by subtracting adipose tissue mass from total body weight, as done previously (13).

Analytical methods. Plasma glucose was measured using glucose oxidase (Yellow Springs Instruments, Yellow Springs, OH). Blood samples for the determination of insulin and FFA concentrations were collected into iced tubes containing EDTA and rapidly centrifuged. The plasma was separated and stored at −80°C. FFA concentrations were measured by a standard enzymatic colorimetric method (14). Measurements of insulin were done by RIA using kits purchased from CIS (Commissariat à l'Energie Atomique, France) as previously reported (15), and urinary nitrogen by the method of Kjeldahl (16).

Calculations. The NPRQ was calculated as follows:

$$NPRQ = NP\dot{V}co_2/NP\dot{V}o_2$$

where $NP\dot{V}co_2$ is the nonprotein $\dot{V}co_2$ (L/min) and $NP\dot{V}o_2$ is the nonprotein $\dot{V}o_2$ (L/min).

$$NP\dot{V}co_2 = \dot{V}co_2 - P\dot{V}co_2$$

where $P\dot{V}co_2$ is the protein $\dot{V}co_2$ (L/min).

$P\dot{V}co_2 = N \times 6.25 \times 0.774$ where $N \times 6.25$ is the grams of protein oxidized per minute, because proteins contain 16% nitrogen.

$NP\dot{V}o_2 = \dot{V}o_2 - P\dot{V}o_2$

where $P\dot{V}o_2$ is the protein $\dot{V}o_2$ (L/min).

The fraction of $NP\dot{V}o_2$ as a result of glucose oxidation is

$F_{glu} = [NPRQ - 0.705]/[1 - 0.705]$

and the fraction as a result of fat oxidation is

$F_{fat} = 1 - F_{glu}$.

The rates of glucose and fat oxidation (in g/min) were calculated from the following equations:

Glucose oxidation = $F_{glu} \times [NP\dot{V}o_2/0.746]$

Fat oxidation = $F_{fat} \times [NP\dot{V}o_2/2.03]$

Statistical analysis. All data are presented as means ± SE. The statistical comparisons between obese and control groups were calculated with the unpaired Student's *t* test.

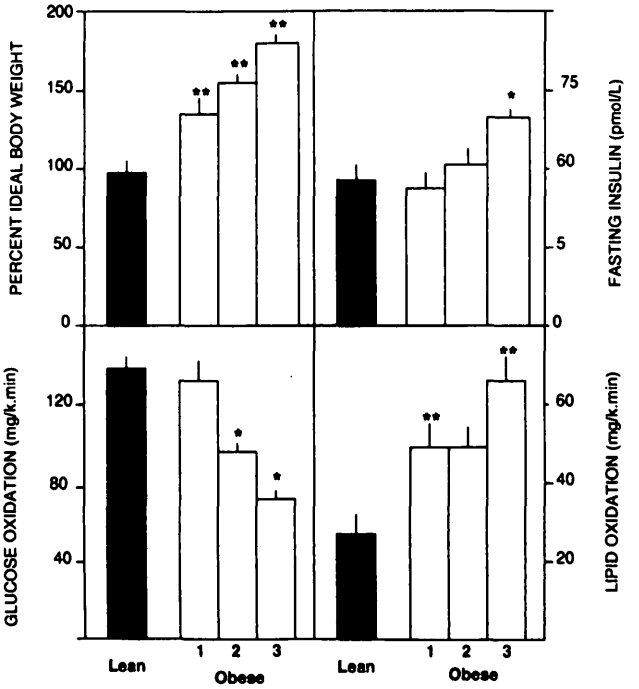

FIG. 1. Mean values of IBW, fasting plasma insulin concentration, glucose oxidation, and lipid oxidation in normal children and in three groups of patients with obesity of various duration: group 1, 1–4 yr; group 2, 4–7.5 yr; group 3, 7–11.5 yr. *P < 0.05, **P < 0.01.

RESULTS

Body size increase. The group of obese children showed a significant correlation between the duration of obesity and the parameters reflecting the increase of body size: body weight ($r = 0.69$, $P < 0.0005$), percentage of IBW ($r = 0.57$, $P < 0.001$), and body surface ($r = 0.66$). For LBM, $r = 0.70$ and for fat mass $r = 0.69$. The rate of weight accumulation, however, was independent of obesity duration, i.e., a patient with prolonged obesity gain gained weight at a rate comparable to a patient with a shorter history of obesity.

Plasma insulin changes. The overall mean basal insulin value (64 ± 5 pM) was not different from that in normal age-matched children (54 ± 4 pM). There was a statistical tendency for increasing basal plasma insulin with obesity duration ($r = 0.48$, $P < 0.01$), independent of age. Mean fasting plasma insulin was found to be higher than normal only after 7 yr of obesity (Fig. 1). Fasting insulin levels also correlated with the degree of obesity, although to a lesser extent than with obesity duration. No correlation was found between fasting insulin level and the pubertal stage of the obese children of this study.

Basal energy production. Basal energy expenditure was near normal in the first years of obesity, then increased with the duration of obesity ($r = 0.54$, $P < 0.005$) in relationship with increased body mass ($r = 0.81$, $P < 0.0001$) and BSA ($r = 0.81$). The slope of the regression line was ~11.5 kcal/kg body wt, which means that for each kilogram of excess body weight the overall energy expenditure is increased by 11.5 kcal/day. This resulted in a mean energy expenditure of 1.13 ± 0.04 kcal/min in the obese group versus 0.96 ± 0.03 kcal/min in normal children ($P < 0.005$).

Obese children derived only 39 ± 3% of their energy needs from the oxidation of glucose, instead of the normal 67 ± 6% ($P < 0.0005$). This was associated with a predominant oxidation of fat in the obese (61 ± 6 vs. 33 ± 3%). The NPRQ, calculated from measurements of $\dot{V}o_2$ and $\dot{V}co_2$, was decreased in the obese group: 0.82 ± 0.01 vs. 0.90 ± 0.02 in normal children ($P < 0.0005$). The evolution toward oxidation of less carbohydrate versus fat was found dependent on the duration of obesity ($r = 0.54$, $P < 0.01$).

Pubertal stage had no apparent influence on energy expenditure or on the relative rates of carbohydrate or lipid oxidation.

Increased lipid oxidation. Lipid oxidation was increased twofold in the obese (56 ± 4 mg/min) compared with normal children (25 ± 5 mg/min, $P < 0.0005$). The increase in lipid oxidation was already present in the patients with the shorter duration of obesity and despite a positive correlation ($r = 0.52$, $P < 0.01$) showed little additional increase with duration of obesity (Fig. 1). This could simply reflect the augmentation of fat stores, as suggested by the correlation between fat mass and the rate of lipid oxidation ($r = 0.48$, $P < 0.01$). Normalization of lipid oxidation to body weight, surface area, lean and fat mass, or basal energy expenditure confirmed the difference with normal children (Table 2) but did not reveal any correlation with duration of obesity. Lipid oxidation correlated with plasma FFA concentrations ($r = 0.58$, $P < 0.01$). Lipid oxidation changes showed no relationship with pubertal stages.

Decreased glucose oxidation. Absolute glucose oxidation was 32% lower in the obese (93 ± 6 mg/min) compared with normal children (136 ± 6 mg/min). This decrease was not observed in the patients with the

TABLE 2
Basal energy expenditure and lipid and glucose oxidation in normal and obese children

	Normal children	Obese children	*P* value
n	14	31	
NPRQ	0.90 ± 0.02	0.82 ± 0.01	<0.0005
EPR (kcal/min)	0.96 ± 0.03	1.13 ± 0.03	<0.005
F_{Glu} (%)	67 ± 6	39 ± 3	<0.0005
F_{Lipid} (%)	33 ± 3	61 ± 6	<0.0005
Lipid oxidation			
mg/min	25 ± 5	56 ± 4	<0.0005
mg · m^2BSA^{-1} min^{-1}	20 ± 2	35 ± 2	<0.0005
mg · kg LBM^{-1} · min^{-1}	0.79 ± 0.2	1.64 ± 0.1	<0.0005
mg · $kcal^{-1}$ · min^{-1}	25 ± 3	16 ± 1	<0.05
Glucose oxidation			
mg/min	136 ± 6	93 ± 6	<0.0005
mg · m^2BSA^{-1} · min^{-1}	109 ± 11	58 ± 4	<0.0005
mg · kg LBM^{-1} · min^{-1}	4.5 ± 0.5	2.8 ± 0.2	<0.0005
mg · kcal EPR^{-1} · min^{-1}	137 ± 14	85 ± 5	<0.005

Data are means ± SE. F_{Lipid}, fraction of EPR derived from lipids.

shorter duration of obesity (Fig. 1). Normalization to body weight, BSA, lean body mass, or basal energy expenditure showed a consistent 37–46% decrease of the rate of glucose utilization (Table 2). A strong correlation was found with obesity duration, the patients with the more prolonged obesity having the lower rate of glucose oxidation per kilogram of body weight ($r = 0.71$, $P < 0.005$), kilograms of lean body mass ($r = 0.72$) (Fig 2), per square meters of BSA ($r = 0.64$, $P < 0.001$), or per kilocalorie of basal energy expenditure ($r = 0.64$).

If both were expressed per unit of BSA (Fig. 3) or energy expenditure, glucose oxidation correlated inversely with lipid oxidation ($r = 0.49$, $P < 0.01$ and $r = 0.65$, $P < 0.0005$, respectively).

No significant differences for any measured parameter were observed between girls and boys. We observed no significant negative correlation of glucose oxidation rate with pubertal stages in the obese children, whereas a negative correlation was present in the lean children (Table 3).

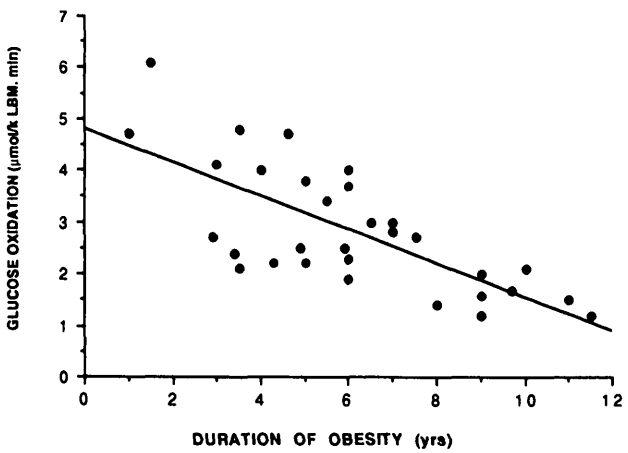

FIG. 2. Evolution of glucose oxidation normalized to LBM with duration of obesity. Inverse relationship is described by $y = -0.33x + 4.8$ ($r = 0.72$, $P < 0.0001$).

DISCUSSION

In obese children, adipose triglyceride lipolysis is approximately double that of normal children corresponding to the mobilization of 180 mg/min of FFAs in the postabsorptive state versus 90 mg in normal subjects (17). In this study, obese children showed a rate of lipid oxidation (56 mg/min) increased in the same proportions compared with normal subjects (25 mg/min). The amount of FFAs oxidized per unit of lean body mass was double in the obese (1.64 ± 0.10 mg · kg LBM^{-1} · min^{-1}) compared with normal children (0.79 ± 0.20 mg · kg LBM^{-1} · min^{-1}). From these values, one could estimate that, in obese as well as in normal children, 30% of mobilized FFAs are oxidized and 70% enter the pathways of nonoxidative metabolism. These pathways include the in situ reesterification of the FFAs mobilized by lipolysis, the synthesis of lipoproteins (18,19), and the accumulation of triglycerides in the skeletal muscles (20). These processes have not been quantified in this study but will be important to determine to obtain a complete picture of lipid fluxes in recent obesity. Because lipoprotein synthesis can only account for a small fraction of the nonoxidative disposal of FFA (18,19,21), the major part of the nonoxidative disposal (124 mg/min) in the obese individual corresponds to both immediate reesterification of FFAs in the adipocytes and lipid storage in muscles. These muscle FFAs and triglycerides are likely to be a source for tissue lipid oxidation (22).

We found that the rate of lipid oxidation was dependent on the fat mass and that lipid oxidation per kilogram of fat mass did not vary with the degree of obesity. These results are different from those obtained in obese Pima women (23), in whom lipid oxidation rates, expressed per kilogram of body fat, decreased with increasing degree of obesity, indicating that, in this model, FFAs were not available for oxidation in proportion to the size of triglyceride stores and that other regulators of lipid oxidation (nonoxidative routes, quality of adipose tissue and its milieu) were of major importance. Besides the specific characteristics of Pima Indians as a racial group, these

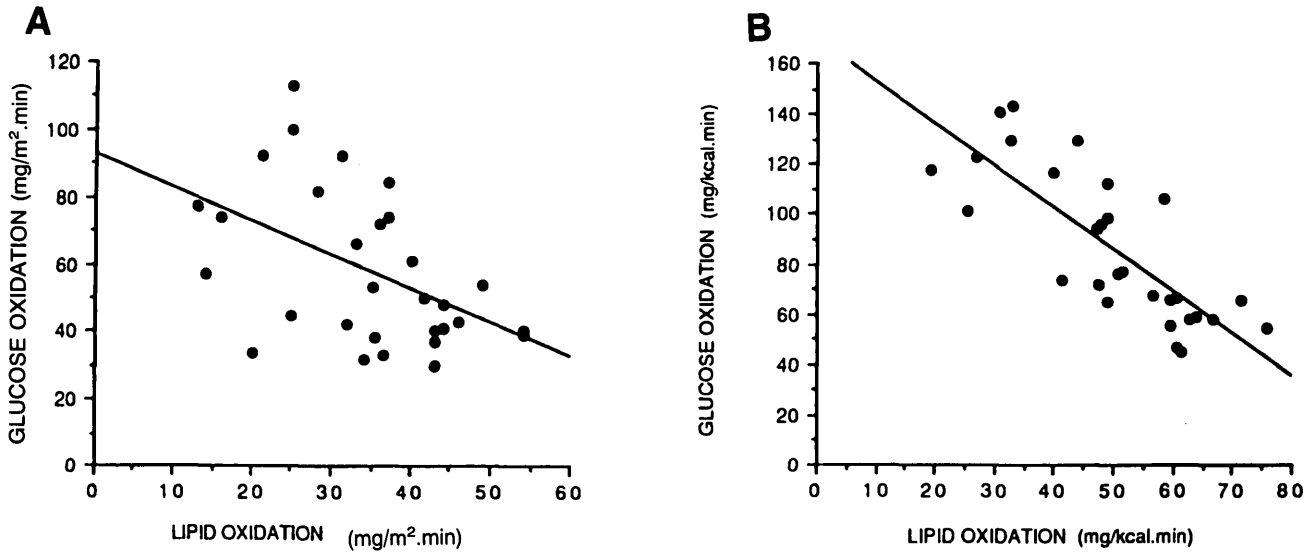

FIG. 3. Inverse relationship between glucose and lipid oxidation in obese children. When normalized to BSA (*A*), relationship is $y = -1.01x + 93$ ($r = 0.49$, $P < 0.01$). A comparable equation describes relationship between same parameters in (24). When normalized to EPR (*B*), relationship is $y = -1.7x + 170$ ($r = 0.79$, $P < 0.0001$).

differences could also be related to the natural history of obesity at the time of study. Long, stable duration of obesity, hyperinsulinism, and insulin resistance were among the distinctive features of these Pima women compared with our obese children.

Because fat metabolism in obese children was oriented toward mobilization (17) and oxidation of lipid stores, no net lipid synthesis occurred in the postabsorptive state. To quantify the mechanisms supporting their continuous and rapid weight increase, the measurement of lipogenesis at time of meals, which has not been attempted yet in this active phase of obesity, will be important to investigate.

Another aspect of this study is the alteration of postabsorptive glucose oxidation in the dynamic phase of human obesity. Decreased glucose oxidation does not appear to be an early defect associated with obesity because its development is delayed by several years compared with the increase in lipid oxidation. Several experimental demonstrations exist that increased fat oxidation by skeletal muscle can decrease glucose oxidation, which could apply to these obese children.

TABLE 3
Glucose oxidation at different stages of puberty

	n	Age (yr)	Glucose oxidation ($mg \cdot m^{-2} \cdot min^{-1}$)
Obese children			
Nonpubertal	12	10 ± 0.5	58 ± 7
Tanner II-III	8	12 ± 0.4	72 ± 7
Tanner IV-V	11	14 ± 0.5	53 ± 7
Lean children			
Nonpubertal	6	9.5 ± 0.2	130 ± 22*
Tanner II-III	3	12 ± 0.3	111 ± 22*
Tanner IV-V	5	15 ± 0.2	92 ± 22†

Data are means ± SE.
*$P < 0.005$.
†$P < 0.0005$ vs. Tanner stage-matched control subjects.

According to Randle et al. (24), an increased supply of FFAs to muscle can restrain glucose transport and disposal through the inhibitory action of the products of FFA oxidation (citrate, adenosine 5′-triphosphate, reduced nicotinamide adenine dinucleotide, acetyl-coA) on key enzymes of glucose metabolism (pyruvate dehydrogenase, phosphofructokinase, hexokinase). By way of this substrate competition, insulin action on glucose metabolism could be impeded secondarily to a derangement in lipid metabolism (25,26). The progressive augmentation of fat stores and lipid oxidation during the first years of obesity could therefore induce a progressive decrease of glucose oxidation and decreased insulin action. Our observations are no proof, however, that these phenomena are causally related.

In normal humans, glucose oxidation represents the major route of postabsorptive glucose utilization. Consistently, in normal children with glucose utilization rates of 120–140 mg/min (13), these results found rates of glucose utilization averaging 136 mg/min. In recently obese children with supranormal glucose utilization rates of 295 mg/min (13), only 93 mg/min of glucose were found to be oxidized. These results indicate that nonoxidative routes of glucose utilization in the postabsorptive state are largely increased in recent obesity. These routes include glucose storage as glycogen, anaerobic glycolysis leading to lactate production, and lipogenesis. This study does not allow for evaluation of these nonoxidative metabolic pathways in obese children. The conversion of glucose to lactate can have several sources. The conversion may occur in skeletal muscle and heart as a consequence of privileged lipid oxidation or as a result of inhibition of pyruvate dehydrogenase by acetyl-CoA and the resulting decrease of pyruvate oxidation (27). In addition, lactate production can also occur in adipose tissue (28,29). According to an estimate based on microdialysis in vivo, the release of lactate by this tissue reaches 1 $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$ in normal humans (29).

If this value was (without experimental validation) extrapolated to our patients having 29 kg of fat mass, lactate production by adipose sites would reach 290 μmol/min and with the assumption that this lactate source is predominantly glucose, would imply that ~25–30 mg of glucose escape oxidation in the adipocytes and are recycled as lactate. To remain included in nonoxidative glucose metabolism, lactate should be cycled back to glucose by the liver. The hypothesis of excess glucose-lactate cycling fluxes in obese children, consistent with their increased glucose production (13) and decreased glucose oxidation, should be tested in future experiments.

Basal energy production was increased in the obese children, showing a close correlation with body size. In the absence of previous data regarding the active phase of human obesity, this is the first indication that abnormal weight increase is not caused by decreased energy expenditure, at least in the fasting state. The obese children of this study were gaining weight at a rapid rate while expending 15% more energy than their normal control subjects. Glucose accounted for only 39% of their basal energy production versus 66% in age-matched lean children. The contribution of carbohydrate oxidation to basal energy production decreased as obesity progressed. The subsequent energy deficit was overcompensated by lipid oxidation, resulting in an energy production increase of 11.5 kcal/day for each kilogram of excess weight. If normalized to body surface, energy production was slightly, but significantly, diminished a likely consequence of the modification of body composition toward a predominant adipose tissue mass less active metabolically.

Postabsorptive energy metabolism during the first years of obesity is characterized by an early increase in lipid oxidation, followed by a progressive decrease in glucose oxidation. This results in obese children deriving 61% of their energy production from lipids compared with lean children who derive 66% of their energy from carbohydrates. These changes occur without detectable modifications in plasma insulin levels. In adult patients with established obesity, lipid oxidation remains higher than in control subjects, both in the postabsorptive state and after an oral glucose load (30,31).

In conclusion, these data should be examined in the context of two studies that indicated that lipid oxidation may be enhanced in obese subjects, in association with decreased glucose oxidation. In 18 nondiabetic obese Pima Indian women 18–35 yr of age, basal lipid oxidation and glucose oxidation rates averaged 27 and 47 $mg \cdot m^{-2} \cdot min^{-1}$, respectively, and showed inverse linear correlation (26). In 24 obese adults (8 men, 16 women) 28 ± 2 yr of age, whose glucose tolerance was within normal limits, basal lipid oxidation averaged 38 $mg \cdot m^{-2} \cdot min^{-1}$ (vs. 31 $mg \cdot m^{-2} \cdot min^{-1}$ in lean controls) and glucose oxidation 48 $mg \cdot m^{-2} \cdot min^{-1}$ (vs. 62 $mg \cdot m^{-2} \cdot min^{-1}$ in lean controls; 25). An inverse correlation ($r = -0.48$) was found between these rates when the data from these obese subjects were pooled with those from other obese patients with impaired glucose tolerance ($n = 23$) or overt diabetes mellitus ($n = 35$) (24). Both studies discussed the possibility that the impairment in glucose metabolism was caused by an excessive utilization of fatty substrates, as proposed by Randle et al. (32). The conditions on which Randle's hypothesis can hold in clinical research are *1*) lipid oxidation is increased; *2*) glucose oxidation is decreased; and *3*) the two changes are commensurate to one another (1). The hypothesis is therefore consistent with our observations in recently obese children. Compared with previous studies, these subjects were analyzed at an earlier phase of obesity, reflected by their younger age, recent and progressing obesity, and normal fasting insulin levels. This provided the opportunity to document that the increase in lipid oxidation preceded the changes in glucose oxidation and insulin levels associated with long-duration obesity. The sequence of events in these obese children suggests that the coexisting alterations described by previous authors are involved early in the natural history of obesity.

ACKNOWLEDGMENTS

We thank J. Lalau-Keraly, whose patients participated in the study, and C., L., F., and A. Bougnères; P.Y., D., and G. Bourgeois; C. Crevaux; J. Boitard; and their friends for participating as the control subjects.

REFERENCES

1. Golay A, Felber JP, Jéquier E, DeFronzo RA, Ferrannini E: Metabolic basis of obesity and noninsulin-dependent diabetes mellitus. *Diabetes Metab Rev* 4:727–47, 1988
2. Pedersen O: The impact of obesity on the pathogenesis of non-insulin-dependent diabetes mellitus: a review of current hypotheses. *Diabetes Metab Rev* 5:495–509, 1989
3. Horton ES, Jeanrenaud B: Obesity and diabetes mellitus. In *Diabetes Mellitus, Theory and Practice.* Rifkin H and Porte D, Eds. New York, Elsevier, 1990, p. 455–63
4. Felber JP, Meyer HU, Curchod B, Iselin HU, Rousselle J, Maeder E, Pahud P, Jéquier E: Glucose storage and oxidation in different degrees of human obesity measured by continuous indirect calorimetry. *Diabetologia* 20:39–44, 1981
5. Felig P, Cunningham J, Levitt M, Hendler R, Nadel E: Energy expenditure in obesity in fasting and postprandial state. *Am J Physiol* 244:E45–51, 1983
6. Simic BS: Childhood obesity as a risk factor in adulthood. In *Childhood Obesity.* Collip PJ, Ed., Littleton, MA, PSG, 1980, p. 3–23
7. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–57, 1979
8. Boggio V, Klepping J: Caractéristiques de la ration alimentaire de l'enfant. Résultats d'enquêtes effectuées chez des enfants de 5,10, et 15 ans dans l'agglomération dijonnaise. *Arch Fr Pédiatr* 38:679–86, 1981
9. Dupin H et les membres de la Commission du Centre National de Coordination des Etudes et Recherches sur l'Alimentation et la Nutrition (CNERNA). *Apports Nutritionnels Conseillés Pour la Population Française.* Paris, Technique et Documentation, 1981
10. Hernesniemi I, Zachman M, Prader A: Skinfold thickness during infancy and adolescence: a longitudinal correlation study in normal children. *Helv Paediatr Acta* 29:523–28, 1974
11. Deurenberg P, Pieters JJL, Hautvast JGAJ: The assessment of the body fat percentage by skinfold thickness measurements in childhood and young adolescence. *Br J Nutr* 63:293–303, 1990
12. Slaughter MH, Lohman TG, Boileau RA: Skinfold equations for estimation of body fatness in children and youth. *Hum Biol* 60:709–23, 1988
13. Bougnères PF, Artavia-Loria E, Henry S, Basdevant A, Castano L: Increased basal glucose production and utilization in children with recent obesity versus adults with long-term obesity. *Diabetes* 38: 477–83, 1989
14. Itaya K, Ui M: Colorimetric determination of free fatty acids in biological fluids. *J Lipid Res* 6:16–20, 1965
15. Bougnères PF, Ferré P, Chaussain JL, Job JC: Glucose metabolism in hyperinsulinemic infants: the effects of fasting and sodium DL-β-

hydroxybutyrate on glucose production and utilization rates. *J Clin Endocrinol Metab* 57:1054–60, 1983
16. Hawk PB: Kjeldahl method. In *Practical Physiological Chemistry*. 12th ed. Toronto, Blakiston, 1947, p. 814–22
17. Le Stunff C, Bougnères PF: Glycerol production and utilization during the early phase of human obesity. *Diabetes* 41:444–50, 1992
18. Havel RJ, Kane JP, Balasse EO: Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglycerides of very low density lipoproteins in normotriglyceridaemic and hypertriglyceridemic humans. *J Clin Invest* 49: 2017–35, 1970
19. Howard BV, Zech L, Davis M: Studies of very low density lipoprotein triglyceride metabolism in an obese population with low plasma lipids, lack of influence of body weight or plasma insulin. *J Lipid Res* 21:1032–41, 1980
20. Carlson LA, Liljedakl SO, Wirsen C: Blood and tissue changes in the dog during and after excessive free fatty acid mobilization. *Acta Med Scand* 178:81–102, 1965
21. Miller HI, Bortz WM, Durham BC: The rate of appearance of FFA in plasma triglyceride of normal and obese subjects. *Metabolism* 17:515–21, 1968
22. Dagenais GR, Tancredi RG, Zierler KL: Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. *J Clin Invest* 58:421–31, 1976
23. Lillioja S, Foley J, Bogardus C, Mott D, Howard BV: Free fatty acid metabolism and obesity in man: in vivo in vitro comparison. *Metabolism* 35:505–14, 1986
24. Randle PJ, Kerbey AL, Espinal J: Mechanisms decreasing glucose oxidation in diabetes and starvation: role of lipid fuels and hormones. *Diabetes Metabol Rev* 4:623–38, 1988
25. Felber JP, Ferrannini E, Golay A, Meyer HU, Theibaud D, Curchod B, Maeder E, Jéquier E, DeFronzo RA: Role of lipid oxidation in pathogenesis of insulin resistance of obesity and type II diabetes. *Diabetes* 36:1341–50, 1987
26. Lillioja S, Bogardus C, Mott DM, Kennedy AL, Knowler WC, Howard BV: Relationship between insulin-mediated glucose disposal and lipid metabolism in man. *J Clin Invest* 75:1106–15, 1985
27. Randle PJ, Newsholme EA, Garland PB: Regulation of glucose uptake by muscle: effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. *Biochem J* 93:652–65, 1964
28. Marin P, Rebuffe-Scrive M, Smith U, Bjórntorp P: Glucose uptake in human adipose tissue. *Metabolism* 36:1154–60, 1987
29. Jansson PA, Smith U, Lönnroth P: Evidence for lactate production by human adipose tissue in vivo. *Diabetologia* 33:253–56, 1990
30. Jéquier E, Felber JP: Indirect calorimetry. In *Baillière's Clinical Endocrinology and Metabolism. Techniques for Metabolic Investigation in Man*. Alberti KG, Home PD, Taylor R, Eds. London, Baillière Tindall, 1987, p. 911–35
31. Golay A, Felber JP, Meyer HU, Curchod B, Maeder E, Jéquier E: Study on lipid metabolism in obesity diabetes. *Metabolism* 33:111–18, 1984
32. Randle PJ, Garland PB, Hales CN, Newsholme EA: The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1:785–89, 1963