Blunted Glucose Metabolism in Anorexia Nervosa

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Only few studies have specifically investigated diet-induced thermogenesis in anorexia nervosa. Twenty women, 10 anorectics (body mass index [BMI] = 14.98 ± 1.02 kg/m^2) and 10 controls (BMI = 22.53 ± 0.75 kg/m^2) were studied. Body composition was evaluated by isotopic dilution. Respiratory gas exchange was measured by indirect calorimetry. An oral glucose load (75 g) was administered to the anorectics (A) and the controls (CA). The controls underwent a second load (CB) with a higher glucose amount (1.85 ± 0.11 g/kg body weight [BW]) to compare with the load taken by anorectics. Glucose-induced thermogenesis (GIT) was computed for 300 minutes following the load as the percent increase of energy expenditure (EE) above resting-EE (REE). Serum glucose levels were lower in anorectic patients both in fasting (3.46 ± 0.66 *v* 5.23 ± 0.23 in CA, *P* < .01 *v* 5.32 ± 0.34 mmol in CB, *P* < .01) and in the postprandial state (glucose area under the curve [AUC] 175.51 ± 6.40 *v* 289.80 ± 7.30 in CA, *P* < .01 *v* 324.65 mmol in CB, *P* < .001); insulin AUC was lower, 1,926 ± 452 versus 41,148 ± 2,071 in CA, *P* < .0001 versus 60,765.5 pmol in CB, *P* < .0001. REE, normalized by fat-free mass (FFM), was similar between groups. GIT was lower in anorectics (3.58 ± 1.20 *v* 5.45 ± 1.83 in CA, *P* < .05 *v* 9.09% ± 1.05% in CB, *P* < .01). Glucose oxidation was higher in anorectics than in CA (689.44 ± 72.22 *v* 333.32 ± 32.98 μmol/L/min, *P* < .001), but similar to CB. Lipid oxidation become negative after 30 minutes in anorectics (postprandial lipid oxidation = -93.58 ± 39.86 *v* 370.61 ± 21.73 in CA, *P* < .0001 *v* 119.01 ± 12.32 μmol/L/300 min in CB, *P* < .0001). Anorectic patients displayed a low REE and GIT. Carbohydrate oxidation was similar between groups; lipid oxidation was extremely reduced. An increased protein catabolism was observed.

ANOREXIA NERVOSA IS A syndrome characterized by severe body weight loss, obsession for weight gain, cessation of menstruation, as well as other neuroendocrine disorders.[1] Although a great deal of attention has been focused on the psychiatric aspect of this syndrome, due primarily to its increasing prevalence in western countries, its metabolic aspects have not been clearly elucidated.

In anorexia nervosa, energy expenditure and substrate metabolism have been evaluated both during food restriction and weight gain periods with disparate results. Normal overall daily energy expenditure[2,3] and lower basal metabolic rates have been reported in restricted anorectic patients, probably due to the high physical activity levels of subjects under study. Conversely, other investigations reported normal levels of resting energy expenditure (REE)[4] without considering the total energy expenditure. A decrease of REE has been described also in the early refeeding states and during the target weight stabilization period of anorexia nervosa, probably caused by the subsequent reduction of energy intake after the weight gain period.[5] On the other hand, during the late refeeding period, REE becomes comparable to that of the control subjects, in view of the enhanced energy intake during the refeeding period. The increased metabolic needs during this period have been ascribed also to an increase of diet-induced thermogenesis (DIT).[6] However, the contradictory results of the few investigations on this topic show a normal,[2] higher,[7] or even lower[8] thermic response to a mixed meal. To our knowledge, only 1 study deals with the glucose-induced thermogenesis (GIT) in anorexia nervosa, which reports a higher response to an oral glucose load compared with control subjects.[7]

An impaired glucose metabolism has been observed in anorectic patients, so that a modified fuel oxidation could be expected in these patients. In fact, previous studies have already demonstrated a low insulin response, high carbohydrate oxidation, and low metabolic rate[7-9] after a 50-g glucose load. The aim of the present study was to investigate, over 5 hours, the GIT and the glucose and insulin responses after a 75-g glucose load in 10 restricted anorectic women compared with 10 normal subjects assuming both a standard glucose load and a glucose amount (1.85 ± 0.11 g/kg body weight [BW]) relative to that administered in anorectics.

SUBJECTS AND METHODS

Ten women with anorexia nervosa (body mass index [BMI] = 14.08 ± 1.02 kg/m^2) and 10 women of normal weight (BMI = 22.53 ± 0.75 kg/m^2) were studied. At that time, the anorectic patients had their food intake restricted and were given a variable daily caloric intake ranging from 2,500 to 3,300 kJ, as it resulted from the daily alimentary diary they were used to recall from the beginning of their therapy at our clinic. At the moment of the experimental session, their weight was stably maintained (± 1 kg) in the month preceding the study. During the previous year, they had been slimmer than in the present period of observation (BMI = 13.28 ± 0.48 kg/m^2); then they gained weight (3.22 ± 0.95 kg) during the first 6 months of the current year under clinical supervision. During the enrollment period, they were again restricted for food. Both anorectic patients and controls were asked to restrain from physical activity during the 10 days preceding the experimental session. The anthropometric and metabolic characteristics of the subjects are shown in Tables 1 and 2. Diagnosis of anorexia nervosa was based on the established criteria of Diagnostic and Statistical Manual of Mental Disorder (DSM IV).[10] The patients were followed as outpatients in the Division of Metabolic Diseases of the Catholic University of Rome, where they had been controlled clinically for at least 10 days before they underwent the study. The healthy volunteers were from the medical staff of the Department. All subjects were evaluated by an alimentary diary for their free-caloric intake. In all subjects, body weight oscillations did not exceed 1 kg during the 10

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Table 1. Anthropometric Characteristics of Anorectic and Control Subjects

	Anorectic Patients	Control Subjects (75 g OGTT)	Control Subjects (1.85 ± 0.11 g OGTT)
Age (yr)	22.34 ± 6.75	25.27 ± 4.88	25.27 ± 4.88
BMI (kg/m^2)	14.08 ± 1.02	22.53 ± 0.75*	22.48 ± 0.85*
FFM (kg)	33.38 ± 1.03	45.54 ± 2.11†	45.41 ± 1.78†
FM (kg)	4.95 ± 1.21	12.18 ± 1.78*	12.21 ± 1.63*
PBF (%)	12.74 ± 3.12	21.10 ± 3.08*	21.19 ± 3.00*
G_0 (mmol)	3.76 ± 0.66	5.23 ± 0.23‡	5.32 ± 0.34‡
I_0 (pmol)	28.83 ± 7.21	21 ± 6.20	34.20 ± 5.20

Abbreviations: PBF, percent of FM; G_0, fasting glycemia; I_0, fasting insulinemia; OGTT, oral glucose tolerance test.

Significance between anorectic patients and healthy controls: * $P <$ .001; † $P <$ .001; ‡ $P <$ .01.

days of enrollment. Each patient gave his informed consent according to the Institutional Review Board guidelines.

Body Composition

The day preceding the experimental session, body weight was measured to the nearest 0.1 kg by a beam scale and height to the nearest 0.5 cm using a stadiometer (Holatin, Crosswell, Wales, UK).

Total Body Water Measurement

Because total body water (TBW) normalized by fat-free mass percentage (FFM%) (TBW/FFM%) was reported to be similar in anorectics relative to normal subjects,[11] body composition was studied by using the isotopic dilution method in our patients, and FFM was obtained by dividing TBW value by 0.732.[12] Fat mass (FM) was then computed as the difference between body weight and FFM. TBW was determined using 0.19 Bq of tritiated water in 5 mL of saline solution administered as an intravenous bolus injection. Blood samples were drawn before and 3 hours after the injected dose. The dpm were counted in duplicate in 0.5 mL of plasma using a Beta-scintillation counter (Model 1600TR; Canberra-Packard, Meriden, CT). Corrections were made (5%) for nonaqueous hydrogen exchange,[13] and water density at body temperature was assumed to be 0.99371 kg/L. Total body water (L) was computed as ^3H_2O dilution space (L) × 0.95 × 0.99371. The within-person day-by-day coefficient of variation was 1.5%.

Oral Glucose Load for GIT Determination

The study was performed after an overnight fast. After voiding, the patients were placed on beds, and a venous catheter was inserted into an antecubital vein for blood sampling; the line was kept patent with saline solution. Respiratory gas exchange measurement was started 40 minutes before the glucose load to measure the REE and continued for 300 minutes after glucose intake to calculate the GIT. At the end of the REE measurement period, a standard 75-g glucose load (which resulted in a load of 1.97 ± 0.12 g/kg BW in anorectic patients (A) and 1.25 ± 0.21 g/kg BW in controls (CA); $P <$ .001) was taken up in less than 3 minutes. To avoid the fact that a difference in the relative glucose load might alter the disposition and the metabolism of the glucose, the same procedure was repeated in the same control group on a different day using an oral glucose load similar to that taken by the anorectic patients (1.85 ± 0.11 g/kg BW (CB) *v* 1.97 ± 0.12 g/kg BW; P = not significant [NS]). Blood samples were collected immediately before the glucose challenge (time 0) and at 10, 20, 30, 40, 50, 60, 80, 100, 120, 140, 160, 180, 210, 240, 270, and 300 minutes postload for serum glucose and insulin determinations. At the end of the experiment, urine was collected for urinary nitrogen and glucose loss assay.

Respiratory gas exchange was measured by an open-circuit ventilated hood system (Deltatrac; Datex Instrumentarium Corp, Helsinki, Finland). Energy balance was computed as the difference between energy intake and energy expenditure. Energy expenditure (EE), non-protein respiratory quotient (npRQ), and substrate oxidation were calculated from oxygen consumption, carbon dioxide production, and nitrogen urinary excretion according to standard formulas.[14] The total glucose oxidation value indicates the amount of glucose oxidized in addition to that converted into lipid. Although the negative value of lipid oxidation is stoichiometrically[14-15] equal to the net amount of fat synthesized,[16] the disappearance rate of lipids is not strictly equivalent to its oxidation rate, and a true measurement of lipogenesis cannot be obtained without independent measures of the de novo lipogenesis.[17] Notwithstanding this, it has generally been assumed that under most circumstances this difference is quantitatively small, and that lipogenesis can occur when lipid oxidation is in excess of lipid synthesis; therefore, it can be calculated as carbohydrate oxidation, independently of the intermediate steps of glucose metabolism. Because 3.16 g is the amount of glucose needed to synthesize 1 g palmitate, we computed the number of grams of carbohydrate converted into lipids during the assay period,[18] considering the results as indicative of a net lipogenesis.

Table 2. Metabolic Characteristics of Anorectic and Control Subjects

	Anorectic Patients	Control Subjects (75 g OGTT)	Control Subjects (1.85 ± 0.11 g OGTT)
REE (kJ/24 h)	4,092.76 ± 434.72	5,731.53 ± 140.84*	5,560 ± 140.09*
REE/FFM (kJ/kg$_{FFM}$/24 h)	122.61 ± 3.67	125.85 ± 3.09	122.66 ± 6.84
Urinary nitrogen loss (g/24 h)	30 ± 9.61	6.31 ± 2.10†	6.31 ± 2.10†
GIT (%)	3.58 ± 1.20	5.45 ± 1.83‡	9.09 ± 1.05*‖
Basal GOX (μmol/min)	222.21 ± 66.63	352.77 ± 66.62	365.00 ± 63.24
GOX$_{300}$ (μmol/300 min)	689.44 ± 72.22	333.32 ± 32.98§	727.97 ± 271.88¶
Basal LOX (μmol/min)	11.11 ± 3.4	259.26 ± 37.04†	271.67 ± 40.08†
LOX$_{300}$ (μmol/300 min)	−93.58 ± 39.86	370.61 ± 21.73†	119.01 ± 12.32§¶
Protein oxidation (g/min)	0.13 ± 0.02	0.03 ± 0.01†	0.03 ± 0.01†

Abbreviations: OGTT, oral glucose tolerance test; REE, resting energy expenditure; GIT, glucose-induced thermogenesis; GOX, glucose oxidation; LOX, lipid oxidation.

Significance between anorectic patients and healthy controls: * $P <$ .01; † $P <$ .0001; ‡ $P <$ .05; § $P <$ .001. Significance between healthy controls (CA and CB): ‖ $P <$ .01; ¶ $P <$ .001.

Biochemical Analysis

Glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer 2; Galway, Ireland) and insulin by the Micro-Particle Enzyme Immunoassay (MEIA, Abbott, Abbott Park, IL).

GIT Calculation

GIT was calculated as the total increase of EE above REE during 300 minutes following the oral glucose challenge using the trapezoidal rule for the calculation of the area under the curve (AUC). GIT was also expressed as percent EE for glucose uptake according to the following equation:

$$\text{GIT} = \frac{\text{EEAUC300 min}}{75\text{g} \cdot 15.67} \cdot 100$$

in which 15.67 kJ is the energy equivalent for 1 g of glucose.[19]

Statistics

All values are expressed as means ± SD. Independent sample *t* test for the unequality of variance was used to assess the significance of differences between means of the examined variables. A linear regression was performed between REE and FFM to ascertain that the intercept value was not significantly different from 0. If this was the case, the REE could be normalized by FFM values. A linear stepwise regression analysis was performed to evaluate the influence of both FM and FFM on GIT.

RESULTS

The daily caloric intake determined from the dietary diary recall during the 10 days preceding the experiment ranged from 2,508 to 3,344 kJ/day in the anorectic patients with a mean of 3,204.44 ± 265.05 kJ/24 hours and an energy balance of -870 ± 250.55 kJ/24 hours. In controls (CA and CB), the free-caloric intake ranged from 5,434 to 7,315 kJ/day with a mean of 6,273.12 ± 638.43 kJ/24 hours, and they had an energy balance of +541.59 ± 356.75/24 kJ/day. In all these situations, energy balance was compatible with a weight modification of ± 1 kg during the 10 days preceding the experiment.

The time course of glucose and insulin concentrations after the oral glucose load is reported in Fig 1. Fasting serum glucose concentration was significantly lower in A relative to both CA (3.76 ± 0.66 *v* 5.23 ± 0.23 mmol; $P < .01$) and to CB (3.76 ± 0.66 *v* 5.32 ± 0.34 mmol; $P < .01$); it was at the low-end, but within the clinically normal range during most of the experiment. In all the groups, serum glucose peaked at 50 minutes following the oral load, then decreased in a similar fashion. The glycemia in anorectic patients remained lower than normal during the entire time course.

Although the fasting serum insulin level was similar in the 3 groups (28.83 ± 7.21 in A, 21.00 ± 6.20 in CA, and 34.20 ± 5.2 pmol in CB; P = NS), the insulin time course was slightly increased, with a flat shape in anorectic patients. The peak of serum insulin was also significantly lower compared with both CA (58.21 ± 6.62 *v* 280.80 ± 28.21 pmol; $P < .0001$) and to CB (58.21 ± 6.62 *v* 498 ± 31.2 pmol; $P < .0001$) (Fig 1).

The plasma glucose AUC was significantly lower in anorectic patients than in controls (175.50 ± 6.41 *v* 289.83 ± 7.30 mmol in CA; $P < .01$ *v* 324.65 ± 8.45 mmol in CB; $P < .005$), as well as the plasma insulin AUC (1,926 ± 452 *v* 41,148 ± 2,071 pmol relative to CA; $P < .0001$ *v* 60,765.5 ± 2,354 pmol relative to CB; $P < .0001$). Control groups showed different serum insulin concentrations after the 2 oral loads (insulin AUC, 41,148 ± 2,071 in CA *v* 60,765.5 ± 2,354 pmol in CB; $P < .05$). The insulin response to the glucose load (ratio of glucose area to insulin area) was significantly higher in anorectic patients than in healthy subjects (0.09 ± 0.01 *v* 0.01 ± 0.00 in CA; $P < .0001$ *v* 0.01 ± 0.00 in CB; $P < .0001$), showing a blunted insulin response in anorectic patients.

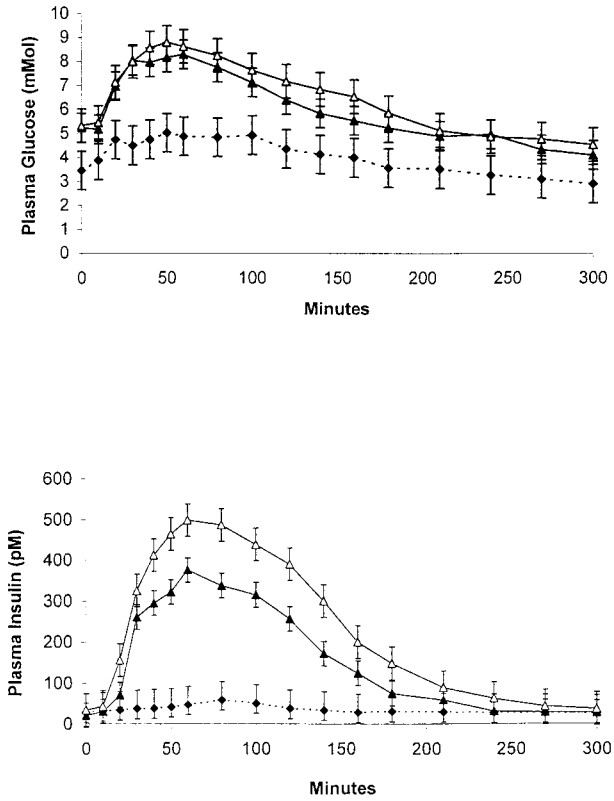

Fig 1. Plasma glucose and insulin concentration before and after the standard (75 g) oral glucose load. Triangles with solid line represent the time courses in control subjects (white triangles, controls assuming 1.85 ± 0.11 g glucose/kg BW; black triangles, controls assuming a standard 75-g glucose), while dashed line represents the time course in anorectic patients.

REE was lower in the anorectic patients (4,092.76 ± 434.72 *v* 5,731.53 ± 140.84 kJ/24 hours in CA; $P < .01$ *v* 5,560 ± 140.09 kJ/24 hours in CB; $P < .01$-); because REE had zero intercept when regressed against FFM ($R^2 = 0.84$; y = 124.48 ×), REE was normalized by FFM. REE/FFM showed little difference between anorectics patients and healthy subjects (CA and CB) (122.61 ± 3.67 *v* 125.85 ± 3.09 kJ/kg$_{FFM}$ in CA; P = NS *v* 122.66 ± 6.84 kJ/kg$_{FFM}$ in CB; P = NS). The GIT, expressed as percentage of the energy content of glucose uptake, was significantly lower in the anorectic group (3.58% ± 1.20% *v* 5.45% ± 1.83% in CA; $P < .05$ *v* 9.09% ± 1.05% in CB; $P < .01$). Using a linear stepwise regression in a model including GIT and BMI, FM and FFM, a positive, linear correlation was found only between GIT and FFM (R = .62,

$P < .001$). The changes in EE after the glucose challenge are shown in Fig 2.

Despite similar basal glucose oxidation in anorectic patients (222.21 ± 66.63 *v* 352.77 ± 66.62 in CA; P = NS *v* 365.00 ± 63.24 μmol/min in CB; P = NS), postprandial glucose oxidation was higher than in CA (689.44 ± 72.22 *v* 333.32 ± 32.98 μmol/300 minutes; $P < .001$), but slightly smaller than in CB (689.44 ± 72.22 *v* 727.97 ± 271.88 μmol/300 minutes; P = NS). Conversely, in anorectic patients, lipid oxidation became negative at 30 minutes and remained negative for the remainder of the experiment (basal lipid oxidation = 11.11 ± 3.4 *v* 259.26 ± 37.04 in CA; $P < .0001$ *v* 271.67 ± 40.08 μmol/minute; $P < .0001$; postprandial lipid oxidation = -93.58 ± 39.86 *v* 370.61 ± 21.73 μmol/300 minutes in CA; $P < .0001$ *v* 119.01 ± 12.32 μmol/300 minutes in CB; $P < .0001$). In addition, anorectic patients showed an earlier peak (50 minutes *v* 100 minutes after the load in both control subjects groups) of glucose oxidation followed by a constant decreasing rate (Fig 3).

Total urinary nitrogen excretion was 30 ± 9.61 versus 6.31 ± 2.10 g/24 hours in controls ($P < .0001$), with a corresponding higher protein oxidation rate in anorectic patients (0.13 ± 0.02 *v* 0.03 ± 0.01 g/minute in control subjects; $P < .0001$).

DISCUSSION

The major findings of our data after the oral glucose load in anorectic patients were: a reduced GIT, correlated with FFM reduction, and a flat and low glycemic and insulinemic time course.

Glucose and insulin time courses resulted in flat, low curves. The glucose time course peaked later related to controls, probably due to the delayed gastric emptying characteristic of anorexia nervosa.[1,20] Furthermore, serum glucose concentrations remained consistently lower with respect to healthy controls (Fig 1). The poor glycemic levels before and after the oral load and the late gastric emptying induced also a plane insulin response to the glucose challenge.

The REE was significantly lower in anorectic patients; however, following FFM normalization, it became similar to that of

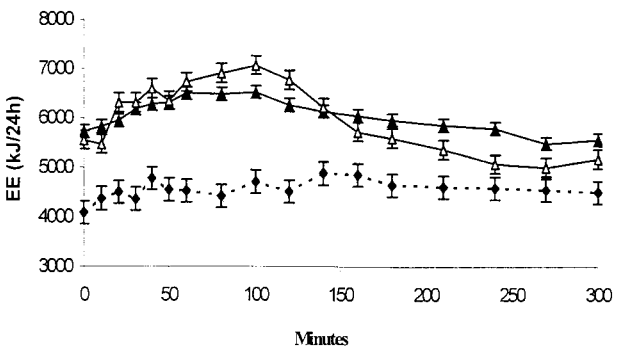

Fig 2. Energy expenditure during the whole experiment. Triangles with solid line represent the time courses in control subjects (white triangles, controls assuming 1.85 ± 0.11 g glucose/kg BW; black triangles, controls assuming a standard 75-g glucose), while dashed line represents the time course in anorectic patients.

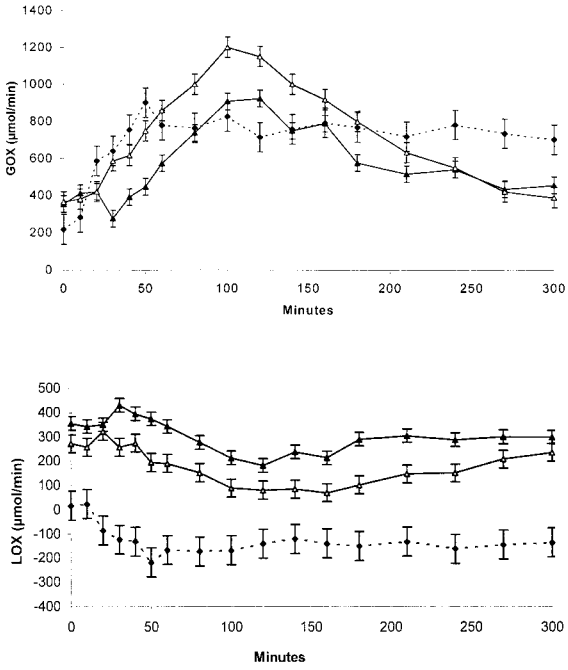

Fig 3. Total glucose and lipid oxidation rate baseline and after the glucose load (75 g). Triangles with solid line represent the time courses in control subjects (white triangles, controls assuming 1.85 ± 0.11 g glucose/kg BW; black triangles, controls assuming a standard 75-g glucose load), while dashed line represents the time course in anorectic patients.

controls. These findings are consistent with other reports.[2,21,22] REE is strongly influenced by both FM and FFM, but mainly by FFM,[23] which can be considered the best predictor of REE. In fact, skeletal muscle influences almost 20% to 25% of REE.[24] The role of FM, which is responsible for only 5% of REE,[25] seems to be mediated by the increased muscular work and cardiac output. Therefore, our findings may reflect FFM depletion and may be useful in predicting weight gain after a dietary normalization.

Despite a similar basal glucose oxidation, postabsorptive glucose oxidation was found to be significantly higher in anorectics than in controls. The higher levels of glucose oxidation could be due to the relative higher levels of glucose assumed by anorectics because of their low body weight. In fact, healthy subjects taking a similar amount of glucose showed similar glucose oxidation rates (Fig 3), but higher glycemic levels. In anorectic patients who have lower glucose levels, this phenomenon can be explained only by an enhanced hepatic glycogen synthesis, as increased hepatic glycogen storage has already been described in anorexia nervosa.[26]

In anorectic patients, the low EE after the glucose load induced a globally low GIT. This phenomenon may be considered as an energy preservation mechanism, which may function to stockpile energy into stores as a consequence of an increased peripheral glucose uptake, similar to that found during euglycemic clamp,[27] followed by an increase in glucose storage. Another possible explanation is that urinary nitrogen does not represent all protein oxidation during the 300-minute GIT

period, and it might also arise from blood urea nitrogen (BUN) from previous protein oxidation caused by the prolonged semistarvation of anorectics' bodies. As a consequence, glucose intake could downregulate protein oxidation, and BUN decreased as clearance exceeded production. Another likely mechanism might be the reduced insulin response observed in anorectics, which can be responsible for a reduced GIT.[28,29]

A reduced thermic effect of glucose has been observed in other conditions opposite to anorexia nervosa, such as type 2 diabetes and obesity. In these situations, GIT reduction is caused by a decreased glucose-substrate availability as a consequence of the insulin resistance,[30] which allows a great reduction of muscular glucose transporter (GLUT-4) expression.[31] In insulin-resistant states, nonoxidative glucose disposal is primarily impaired, with glucose oxidation less affected. In nondiabetic insulin-resistant patients, the response to fasting is a selective suppression in pyruvate dehydrogenase complex in cardiac and skeletal muscle, which likely serves to increase nonoxidative glucose disposal via the storage of glucose as glycogen and lactate production.[32] Although insulin resistance is a common feature of anorexia nervosa,[33,34] some investigators report a normal insulin sensitivity in these patients.[35] Therefore, a mechanism similar to that previously described may only be hypothesized in the absence of lactate measurement.

Anorectic patients had significantly lower levels of lipid oxidation both under basal conditions and after the first minutes of the glucose load as a consequence of the reduced FM of these patients. Beginning with glucose gastric absorption, lipid oxidation became negative, and this finding may be considered indicative of a deranged metabolism, because in healthy subjects, it has been demonstrated that the body is capable of accomodating a carbohydrate excess via conversion to glycogen rather than into fat.[18] Conversely, it is well known that after refeeding, almost 53% of weight gain derives from FM,[11] which increases uniformly without preferential localization,[36] but with a more prevalent subcutaneous compared with visceral distribution.[37]

A great number of other clinical conditions (bed rest, Crohn's disease, celiac disease cancer-induced cachexia, acquired immunodeficiency syndrome [AIDS]) are characterized by body weight loss. In these pathologic situations, the alteration of intermediate metabolism usually occurs as a consequence of FFM depletion due to the malabsorption or to the hypermetabolic state. During a forced bed rest, patients show a reduced lipid oxidation and an enhanced glucose oxidation, with a net lipogenesis,[38] without changes in body composition. A high basal glucose oxidation has also been found in celiac patients before gluten-free diet treatment, along with a depletion of both FM and FFM, probably due to the chronic lipid malabsorption.[39-41] In cancer-induced cachexia, an efficient mobilization and utilization of fat as fuel source,[42] an increased lipid oxidation,[43,44] and an impaired peripheral glucose utilization[45] has been demonstrated.

In conclusion, the prolonged starvation may induce a metabolic derangement with a decreased serum glucose and insulin levels in anorectic patients with a reduced GIT. These metabolic alterations may represent a way to preserve calories by enhancing energy storage.

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