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“Initial hunger” for all? A study on undernourished infants

Abstract

Aim: A meal/satiety pattern dictated by the rhythmic arousal of Initial Hunger (IH and IHMP) is used by overweight people to decrease body weight. We however conceived IHMP to improve intestinal absorption and diminish immune involvement in intestinal mucosa as well as throughout the body (overall subclinical inflammation). The purpose of IHMP may be shown by its early employment in undernourished infants.

Methods: Nine malnourished infants (weight per age lower than 70%) with diarrhea in the first 15 months of age were investigated in a controlled, randomized study. Organic diseases were excluded by conventional procedures, including intestinal biopsy. Six infants were assigned to the intervention and 3 to the control group. Compliance, intake, and anthropometry were recorded in hospital for 2 months, and then by frequent visiting and 7-day home diary under intervention for 5 total times in two years.

Results: Six subjects under intervention and three controls were followed for at least 2 years. Energy intake decreased from 126 ± 21 kcal/kg/d to 85 ± 6 kcal/kg/d in treated infants and from 111 ± 53 kcal/kg/d to 107 ± 37 kcal/kg/d in the first 2 months of study ($P < 0.01$ on longitudinal differences). Days with vomiting became null after 2 months of treatment, whereas in control subjects, 4 or 5 events every 60 days persisted for all follow-ups. Further longitudinal differences were significant on days with diarrhea after three months, and on plasma triglycerides at the two sampled times during treatment. The difference in the Chi square for trend was significant on energy intake and in the numbers of days with vomiting or diarrhea ($P < 0.002$). Serum triglycerides decreased from 148 ± 27 mg/dL to 70 ± 10 mg/dL under intervention, and increased from 119 ± 47 mg/dL to 139 ± 59 mg/dL in controls ($P < 0.002$ on the difference). Values after two years of follow-ups were respectively: 73.2 ± 12.3 mg/dL and 89 ± 37 mg/dL ($P < 0.05$). Toward the end of the study, anthropometric measurements increased per age from recruitment in treated infants with differences from control subjects that were not significant in the longitudinal comparisons between groups. Weight per age reached $88.8 \pm 8.7\%$ under intervention, and $79.7 \pm 10.2\%$ in controls after two years (not significant). Psycho-motor development was normal except for one control infant.

Conclusion: High triglycerides (and associated insulin resistance with an overall subclinical inflammation) are involved in the persistence of diarrhea and on malnutrition in these undernourished infants as in the development of functional bowel disorders and over weight in adults. IHMP was an actual solution also for malnourished infants.

Keywords: malnutrition, energy intake, insulin resistance, hyperglycemia, triglycerides, subclinical inflammation, diarrhea

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Abbreviations: IH, initial hunger; IHMP, initial hunger meal pattern

Introduction

The *raison d'être* of “Hunger Recognition” and of “Initial Hunger Meal Pattern (IHMP)” may be explained by their first employments. This investigation was too restricted for a definitive conclusion on undernourished infants, but may be useful to stimulate further studies on malnutrition and IHMP. The report is sufficient to show that a nutritional and intestinal pathogenesis lies behind malnutrition, persistent diarrhea as well as behind overall subclinical inflammation that is in turn associated with overweight. These dysfunctions depend on a positive energy balance in the associated, parallel-alternative forms of insulin resistance and fattening.¹⁻¹⁸ The intestinal pathogenesis consists of an overgrowth of immunogenic bacteria.^{1,9,12,14,19} Persistent diarrhea has been repeatedly shown to be associated with microflora overgrowth. Fewer than 10 out of 92 luminal aspirates reached the level of about 105 bacteria per ml and 33 were sterile in 9 studies in “healthy” children. Instead, more than 111 out of 187 samplings of

intestinal juice contained over 105 bacteria and only 32 were sterile in 9 studies in children with chronic or persistent diarrhea.¹⁹ Both differences are highly significant. In the small intestinal mucosa, the immune cell number is heavily influenced by bacteria on the mucosa in experimental studies in germ-free animals, and immune activation promotes diarrhea.¹⁻²⁴ Microflora decreased on duodeno-jejunal flat or normal mucosa in the passing time after a meal in children.¹⁹ Our intention was to treat undernourished diarrheic infants by a ‘delay or decrease’ in meal administration. We postponed food administration until arousal of the first hunger manifestation but no longer than this. We have employed this “Hunger Recognition” or “Initial Hunger Meal Pattern” in diarrheic infants who did not show malnutrition, and thus prevented relapses.²⁴⁻²⁸ In the present group of undernourished infants, we report our findings on intake, intestinal manifestations, and anthropometry and on few blood parameters to show that malnutrition depended on an event of insulin resistance and on the associated overall subclinical inflammation.¹⁻⁴¹ The excessive immune stimulation grew as a result of inappropriate food administration. IHMP was the appropriate clinical solution in this controlled, restricted pivotal study.

Methods

Design

The design was a prospective, randomized, controlled, necessarily not-blinded, cohort study in diarrheic, malnourished infants under 15 months of age for 3-18 years. Six subjects under intervention were compared to three control subjects, who were conventionally fed. Energy intake, anthropometric measurements and blood tests, school performances, and symptom prevalence showed functional and nutritional outcomes (Tables 1-5).

Diagnostic criteria

The diagnosis of persistent diarrhea was made in infants with three or more loose stools per day for at least 15 days within the previous three months.⁴² Body weight was expressed in percentage of the median weight at the same age, and malnutrition was diagnosed when the weight per age was lower than 70% in absence of edema, and fewer than 80% in edematous subjects. Celiac disease was excluded on the criteria of the "European Society of Pediatric Gastroenterology and Nutrition".⁴³ Four subjects showed normal villous development in the small intestine mucosal biopsy. The absence of anti-gliadin and anti-endomysium antibodies was periodically documented in all subjects during the follow-up, at least every two years. Further organic disorders, including lactose intolerance, cystic fibrosis, pancreatitis, inflammatory bowel disease, liver and peptic ulcer diseases, and lower respiratory infections or urinary tract infections were excluded. Complete normality in repeated examinations confirmed the diagnosis.

Subjects

Twelve under nourished infants (2-15 months of age) with persistent diarrhea, for more than 15 days, were considered as eligible for the study between the years 1980 and 1996. The infants were concurrently assigned to the intervention or control group in the proportion of three to one. We used this proportion in all children with chronic diarrhea.²⁴⁻²⁸ The assignment was made by use of a concealed sequence prepared on a random-number table.⁴⁴ The intervention group soon recovered from diarrhea,²⁴⁻²⁸ and parents were educated to recognize the 'Initial Hunger (IH)' or 'Initial Demand in children to prevent recurrences. Only three subjects dropped the experimental intervention within one month from recruitment. Their diagnoses were: lymphangiectasia, cystic fibrosis, and Schwachmann Disease. These drop-outs were motivated (reportedly) by family inability to comply with instructions (1) and by a delay in diagnosis (2 and 3). Objectively, these infants' body weight was unchanged compared to the first measurement. Six children participated in the follow-up in the intervention group and three in the control group. One of three control subjects ended the follow-up at 33 months of age for diarrhea and vomiting relapse. No significant difference was found in anthropometric or blood parameters, in intake estimates at recruitment, or in the length of the follow-up between control and treated subjects.

Clinical assessments

Clinical assessments were performed for diagnostic purposes, to assess compliance with the study protocol, to measure food intake, and to evaluate the effects of the training. Adherence to the dietary regimen and physical activity patterns were monitored throughout the observation period by interviewing the principal caretakers by phone (every day initially), clinical visits during follow-up, from the clinical evaluations of the children and diary reports. Clinical assessments included reactive C protein (RCP), standard hematological evaluations, urinalysis, urine culture, examination of stools for occult blood, ova and parasites, antibodies to *H. pylori*, and bacterial

cultures for potential pathogens. Comprehensive biochemical profiles were obtained in all these children. Measurements included serum albumin, hemoglobin, iron, transferrin, calcium, phosphorous, Cu, Zn, total and HDL-cholesterol, triglycerides, alkaline phosphatase, ALT, AST, total IgA, IgM, IgG, antigliadin antibodies, anti tTG and ferritin. Also plasma folate, B12, IgE, red blood cell volume and platelet and eosinophil counts were determined.^{25,27} Anthropometric measurements were obtained by standard techniques as described previously.^{25,27} Individual characteristics and outcomes, and mean (SD) age, weight, length or height, triceps and quadriceps skin fold thickness and corresponding anthropometric NCHS scores are summarized at recruitment and during follow-up in Table 1-6.

Initial Demand Meal Pattern (IHMP; intervention, Table 7)

We asked mothers to suspend food intake for a few hours, and down note the specific manifestations of the child's first food demand.²⁷ Crying, mood changes like loss of enthusiasm for playing, gestural or verbal demand and searching for food without any 'external' stimulus all were considered to be signs of demand (Initial demand, ID or Initial Hunger, IH). Mothers learned ID manifestations. The principal investigator phoned at the end of every first training day to ascertain the actual change made by the mother. A first adherence to this protocol resulted in a mean meal consumption after a delay of two hours (0-48 hours range). At subsequent mealtimes, mothers evaluated arousals according to their first experience to assess if the demands were due to hunger. Our previous studies^{25,27} show that BG is significantly lower in children that demand food than in those who after training do not. We reported the validation of demand recognition previously.²⁵ After training with 42 measurements at hunger arousal, we investigated 16 toddlers not demanding food in comparison with 54 who were demanding for food in the hospital laboratory before breakfast.²⁵ No demand was associated with higher mean BG than the condition of food demand (96.3 ± 10.5 mg/dL vs. 74.6 ± 7.7 mg/dL; $P = 0.0001$). The meaning of this validation in toddlers is that mothers can recognize food request as manifestations that arise at a constant (low) BG in their infants, i.e. corresponding to a physiological identifiable condition. Based on these studies, ID was conceived as a threshold phenomenon triggered by low energy availability in blood indicated by low BG;²⁵⁻²⁷ prior to ID, normal activity is not inhibited by low energy. The intervention may be summarized as a stop of automatic start of eating. This helps to judge constantly the amount to be administered (eaten). At the end of meals, mothers ceased to stop depending on the child's fullness. This dependence deceived toward a prolongation of the satiety interval. Satiety is here an activity without hunger (IH) sensations. Mothers received information on food energy contents, on balance factors, on recommended vegetable intake and physical activity amount *per day*. Half kg per day was the recommended fruit and vegetable amount. The investigators discussed and promoted energy expenditure by decrease in over-heating and over-clothing, and fostering outdoor and gym activities. An absence of IH manifestation before meals was treated in subsequent meals by alternations in behavior that would enhance hunger, such as a decrease in energy-dense food in subsequent meals. It was suggested to avoid snacks was suggested. Earlier than optimal ID was satisfied with fruit. Social obligations like parties and school catering were included in planning the intake amount and in timing the previous and subsequent meals.

Diary compilation

Written records of food intake were collected for 7 consecutive days before any intervention and for five further times to assess dietary compliance, estimate energy and fiber intake. The times

spent at playing and sleeping and daily stool weights were recorded. Caregivers were contacted by telephone at least 7 times between the first two visits to assess the child's feeding behavior and general activity levels.^{25,27} Food intakes were estimated by weighing or measuring food volumes before and after cooking. Measurement utensils were provided to the caretakers by the investigators and all portions served to the child after cooking and leftovers were weighed or measured. All data were recorded on special forms supplied by

the investigators, checked by a dietitian and reported on a computer program. Energy intake was calculated according to McCance.⁴⁵ Energy from unavailable carbohydrates was added to the energy content of the food in the proportion of 2 kcal/g of fiber intake.^{46,47} Each caretaker was instructed in food measurement and weighing by a dietitian during the child's hospitalization. Particular care was suggested for oil added to vegetables.

Table 1 Clinical evaluation at recruitment

Patients	Diagnosis	Associated pathology
Patient 1	Persistent diarrhea	Inborn short small intestine, intervention for volvulus, no resection
Patient 2	Persistent diarrhea	Vomiting
Patient 3	Persistent diarrhea	Preterm, pulm. Fibro dysplasia vomiting, Nissen fundplastic
Patient 4	Salmonellosis	Persistent diarrhea
Patient 5	Small intest. Lymphangiectasia (2 biopsies)	Edema, persistent diarrhea
Patient 6	Persistent diarrhea	Small intestine resection (30cm) for omphalocele
Patient 7	Lymphangiectasia (4small intest. Biopsies)	Edema, persistent diarrhea
Patient 8	Preterm delivery	Intracranial hemorrhage, persistent diarrhea
Patient 9	Salmonellosis, duoden. Biopsy	Persistent diarrhea

Table 2 Additional therapy in the first two weeks after recruitment

Patients	Drug therapy	Parenteral support	Initial food
Patient 1 (1)	Ampicillin, vitamin B	i.v. albumin, 5 d	Human milk
Patient 2	Amoxicillin 10 d		Human milk
Patient 3	Luminal, amoxicillin 15 d	10 d	Mixed \$
Patient 4			Mixed \$
Patient 5	Ampicillin, vitamin B	i.v. albumin, 7 d	Mixed \$
Patient 6		i.v. glucose 5d hemotransfusion 20 ml	Human milk
Patient 7 (2)	Ampicillin, gentalyin; vitamin B,D, C; iron	i.v. albumin, 30 d, transfusion	Mixed £
Patient 8	Gentalyin, vitamin D, E, C, pancreaticenzymes, iron	3 transfusions, PN 15 d	Human milk
Patient 9	Gentalyin 7 d		

(1) Under treatment: mixed meals with 50g - 200g carrot or zucchini, gluten-free cereals plus either chicken or human milk.

(2) Control infants: mixed meals, gluten-free cereals plus either chicken or human milk, without vegetables.

Table 3 Subjects at recruitment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Recruitment Age (m)	4	14	11	14	15	2	8	2	14
Male/Female	m	m	m	f	m	m	m	m	f
Weight (kg)	3.7	7.1	6.0	7.1	7.6	2.4	6.7	3.2	6.3
Weight Per Age (%)	56,1	67.0	61.4	66.2	75.2	48.3	77.3	59.3	68.9
Height Per Age (%)	86.8	97.2	86.9	92.1	96.6	83.5	98.9	87.6	99.3
Sknf Thick n (mm/a)	9.6	12	10.7	15.7	10	5.3	11.3	8.1	6.3
Hb (g/dL)	7.8	10,1	10.6	10.4	11.3	8.1	14.1	10.1	11.5
Albumin (g/dL)	3.4	3.9	3.5	4.3	3.3	3.4	2.1	4.1	3.5
Triglycerides (mg/dL)	135	166	136	182	107	164	86	152	102

Table 4 Anthropometric, functional and nutritional outcomes in six infants under intervention for two years (means \pm SD)

Months Under Intervention	0	2	3	6	11	25
Months of Age	10.0 \pm 5.6	12 \pm 5.4	13.1 \pm 5.8	15.7 \pm 5.8	21.8 \pm 7.6	34.2 \pm 5.5
Energy Intake (Cal/kg/d)	126 \pm 21	85 \pm 6 \pm §	91 \pm 18*	95 \pm 15*	93 \pm 17*	68.0 \pm 8.0*
Weight (kg)	5.6 \pm 2.1	6.1 \pm 2.0	6.7 \pm 1.8	7.7 \pm 1.3	9.6 \pm 1.5*	12.5 \pm 0.8*
Weight Per Age (1)	62.3 \pm 8.9	62.8 \pm 10.6	66.9 \pm 10.6	72.2 \pm 6.7	80.3 \pm 10.0*	88.8 \pm 8.7*
Weight Per Height (2)	79.4 \pm 5.3	82.1 \pm 6.0	82.4 \pm 7.5	88.3 \pm 10.7	93.4 \pm 9.1	97.0 \pm 8.1*
Height (cm)	65.2 \pm 11.4	66.7 \pm 9.9	69.6 \pm 9.2	72.2 \pm 8.7	77.9 \pm 7.4	89.3 \pm 3.8*
Sum of Skinfolds (3)	10.9 \pm 3.4	10.3 \pm 3.6	12.1 \pm 3.5	13.0 \pm 4.4	17.9 \pm 5.7	18.9 \pm 6.3*
Sum of Skinfolds Reference (4)	20.6 \pm 3.7	20.8 \pm 3.6	21.5 \pm 3.0	21.9 \pm 3.7	21.4 \pm 3.2	20.7 \pm 5.7
Sum of Muscle Areas (5)	27.0 \pm 9.2	27.4 \pm 9.8	32 \pm 7.8	36.2 \pm 7.3	45.6 \pm 10.1	60.0 \pm 10.1*
Sum of Areas Reference (4)	45.5 \pm 12.0	47.4 \pm 12.0	49.4 \pm 13.4	53.6 \pm 11.5	62.5 \pm 11.3	70.8 \pm 11.6
Hb (g/dL)	9.7 \pm 1.4			11.1 \pm 1.5		12.8 \pm 0.9*

Table Continued...

Months Under Intervention	0	2	3	6	11	25
MCV (mcr ³)	79.8±7.7			71.3±9.2		77.0±3.1
Albumin (g/dL)	3.6±0.6			3.9±0.4		4.1±0.5
Triglycerides (mg/dL)	148±27			70±9.6*§		73.2±12.3*§
transf. saturation (%)	22.9±10.7			16.6±9.3		22.2±9.4
Alaninaminotransf. (U/L)	79.2±80.6			38.0±21.0		21.0±10.9

(1) = % of mean body weight reference for the same age, NCHS, USA.

(2) = % of mean body weight reference for the same height, NCHS, USA.

(3) = tricipital plus quadripcital skinfold thickness.

(4) = reference for the same age, NCHS, USA.

(5) = tricipital plus quadripcital muscle area, calculated [27].

* = Significant vs Recruitment. § Significant on decreases vs Control group.

Table 5 Anthropometric, functional and nutritional outcomes in three control infants followed for two years

Months Under Intervention	0	2	3	7	11	29
Months of age	7.3 ± 4.0	9.3 ± 4.0	10.7 ± 4.2	14.7 ± 6.0	18.0 ± 6.1	36.7 ± 5.5
Energy intake (Cal/kg/d)	111±53	107±37	106±34	125±48	114±16	78±22
Body weight (kg)	5.4 ± 1.9 (SD)	6.0 ± 1.3	6.3 ± 1.1	7.7 ± 0.7	8.2 ± 0.7	11.5 ± 1.2 *
Weight for age (1)	66.6 ± 12.1	66.9 ± 5.2	67.5 ± 3.3	73.9 ± 1.2	74.1 ± 3.0	79.7 ± 10.2
Weight for height (2)	75.4 ± 5.2	76.6 ± 4.9	76.6 ± 3.9	81.0 ± 2.2	81.0 ± 3.4	86.5 ± 5.8
Height (cm)	65.3 ± 10.3	67.9 ± 8.1	69.5 ± 6.7	74.3 ± 5.5	77.1 ± 4.6	90.8 ± 2.2 *
Sum of skinfolds (3)	11.4 ± 3.3	12.1 ± 2.6	12.6 ± 2.2	14.3 ± 2.4	14.3 ± 2.4	15.0 ± 1.6
Sum of muscleareas (4)	26.6 ± 10.3	28.2 ± 8.0	29.1 ± 6.8	32.3 ± 4.3	35.0 ± 4.5	50.6 ± 6.3 *
Hb	11.9 ± 2.0			11.4 ± 0.4		12± 0.7
Mcv	83.3 ± 6.7			78.7 ± 8.6		79.3 ± 2.1
Albumin	3.2 ± 1.0			4.0 ± 0.3		3.9 ± 0.9
Triglycerides	119 ± 47			139 ± 59		89 ± 37
Transf. Saturation (%)	41.0 ± 26.8			18.0 ± 8.9		23.9 ± 11.8
Alaninaminotransf.	52.7 ± 46.6			35.3 ± 28.3		30.3 ± 30.9

(1) = % of mean body weight reference for the same age, NCHS, USA.

(2) = % of mean body weight reference for the same height, NCHS, USA.

(3) = tricipital plus quadripcital skinfold thickness

(4) = tricipital plus quadripcital muscle area, calculated [27].

* = significant vs recruitment.

Table 6 Last functional and nutritional outcome

	Last Age	Results	Weight	Weight/Age	Height	Height/Age
Patient 1	18 y	High School Diploma	54.3	75.6	161	91.1
Patient 2	10 y	Elementary Student	29.3	93.2	139	101.1
Patient 3	3 y	100 words	12.8	88.6	86	91.3
Patient 4	15 y	High School Student	38	60.8	153	88.0
Patient 5	10 y	elementarystudent	21.3	70.7	124.5	92.4
Patient 6	16 y	High School Student	61.4	99.0	173	99.7
Patient 7	33 m	Walking at 18 Months	11	78.2	88.5	95.5
Patient 8	4.9 y	Hypertension, Convulsion, Death	19	104.5	104.5	96.5
Patient 9	15 y	High School Student	42.9	84.8	153	95.3

Table 7 Training Initial Demand (ID or IH)

- 1 Suspension of meals for up to 48 hours until
- 2 Arousal of physical sensation (manifestation) of hunger
- 3 Measurement of blood glucose concentration (BG)
- 4 Taking note of the physical sensation (manifestation) and associating it mentally with the measured BG
- 5 Taking a meal of about 300 kcal, 150 in children
- 6 Repeat 1-5 increasing the meal size in proportion to the desired inter-meal interval
- 7 Repeat the above procedure for two weeks. At each arousal of physical hunger; compare the sensation (manifestation) and the measured BG with the previous sensations (manifestations)

Statistical analyses

Data are presented as mean \pm SD. The statistical significance of mean changes in values of interest (e.g. energy intake) between pre and post dietary interventions was calculated using a T-test at a 95% confidence level. The rarity of malnutrition in diarrheic, not celiac infants suggested recruiting as many subjects as possible. Bonferroni correction was considered but unnecessary in a follow-up design. Chi square for trends was instead carried out to assess the effects of treatments over time.

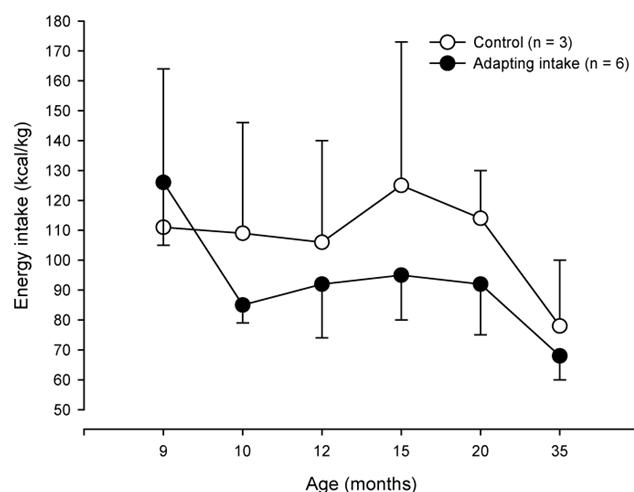


Figure 1 Daily energy intake in treated (6, black circles) and control (3, white circles) subjects during two follow up years. $P < 0.05$ in the longitudinal comparison between decreases from the assessment at recruitment and subsequent assessment.

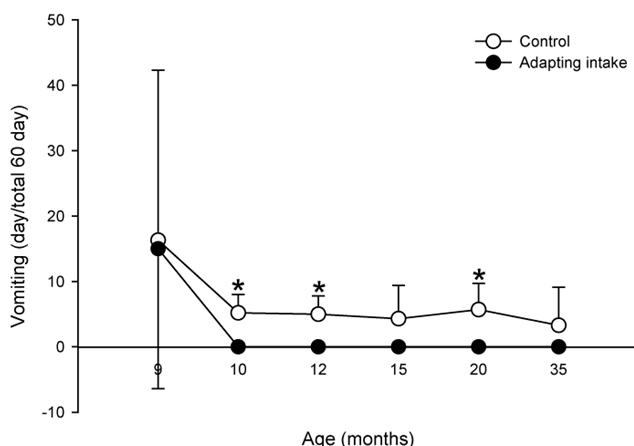


Figure 2 Asterisks show significant difference between groups at that assessment.

Results

We administered gluten-free food for 3 -12 months and repeatedly measured tTG, anti-endomysium antibodies and performed intestinal biopsies after 3 months from gluten reintroduction (Tables 1 & 2). We found no evidence of celiac disease. One treated subject and one control subject showed intestinal lymphangiectasia. Another treated subject with another control subject showed salmonella in feces. At recruitment, all subjects had more than 15 days of diarrhea in the previous 2 months (Table 1). Energy intake decreased from 126 ± 21 kcal/kg/d to 85 ± 6 kcal/kg/d in treated infants and from 111 ± 53 kcal/kg/d to 107 ± 37 kcal/kg/d in the first 2 months of study ($P < 0.01$). During all follow-ups, the longitudinal comparisons on the decreases

were significant between groups on energy intake after 2 months, on days with diarrhea after three months, and on plasma triglycerides at the two sampled times during treatment (Table 4-5, Figure 1-3). Days with vomiting or diarrhea became null after 2 months of treatment, whereas in control subjects, 4 or 5 days with vomiting remained every 60 days for all follow up ($P < 0.002$, Chi square for trend; Figure 2,3). Anthropometric measurements per age significantly increased in treated infants from recruitment to the end of the study (Table 4, Figures 4-6). The treatment poorly affected the psycho-motor.

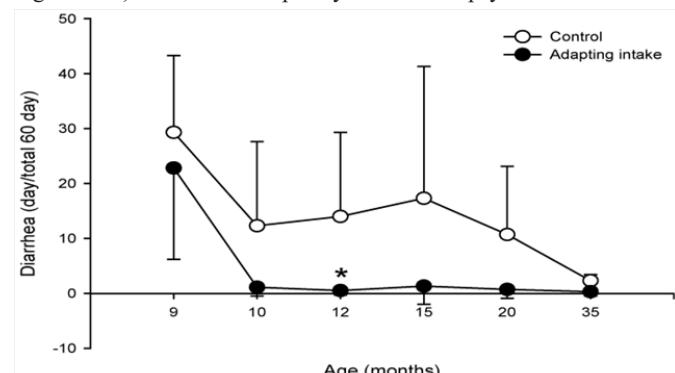


Figure 3 Symbols like in Figure 1 and 2.

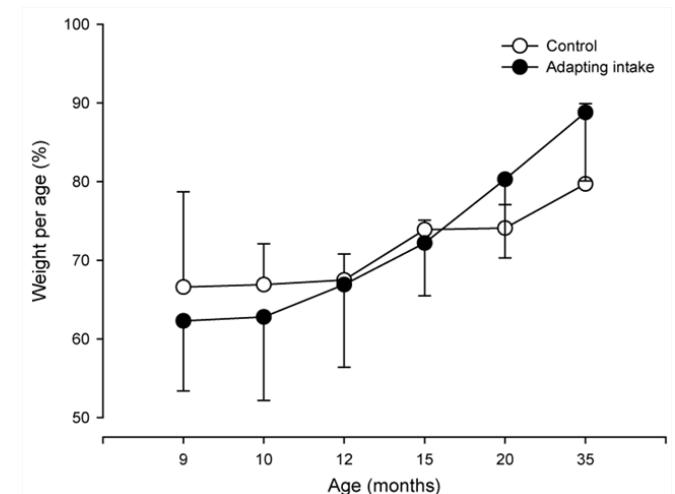


Figure 4 Symbols like in Figure 1 and 2.

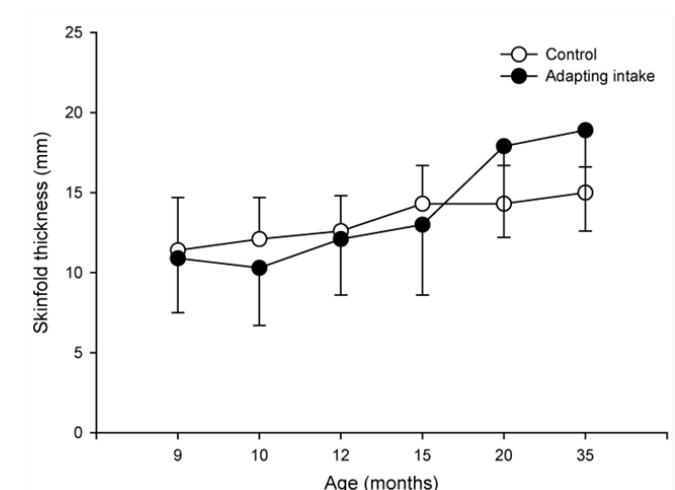


Figure 5 Symbols like in Figure 1 and 2.

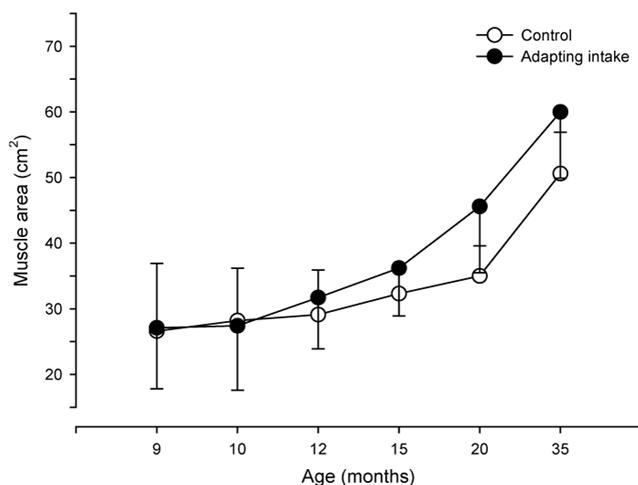


Figure 6 Symbols like in Figure 1 and 2.

Discussion

The Pediatric Gastroenterology Unit of the University of Florence had, as an early commitment, to treat undernourished children with diarrhea and often malabsorption. An adaptation of intake to the pathology-physiology of the alimentary canal was thought to be a solution. Inflammatory stimuli on the small intestinal mucosa might be the main pathological-physiological culprit. Half inflammatory cells of the body originate in this mucosa, 1 and 10%-15% of bacteria in the canal are capable of immune stimulation in proportion to their growth and permanence of energy rich food in the lumen.^{15,19} A shortage of nutrients lowers bacteria on the intestinal mucosa.¹⁹ Absorption rate is variable depending on expenditure and insulin resistance.⁴⁸⁻⁵¹ Undernourished, diarrheic children badly needed the best meal by meal adaptation of intake to their poor absorptive capabilities. Absorption time and permanence of food in the small intestine had to be shortened as much as possible. In this intention we wanted to prevent any sufferance to the children. We decreased food administration to the point of hunger arousal every three hours with maintenance of body growth in this as well as in previous studies.^{25,27,52} We created a meal/satiety pattern that was dictated by the rhythmic arousal of Initial Hunger (IH and IHMP).²⁴⁻²⁸ The Unit prospectively diagnosed, treated by IHMP, recorded treatment and effects in all the children that arrived to the Gastroenterology Unit. All of them were assigned to either treatment by IHMP and control subjects in proportion of three to one. The eligibility criteria for recruitment consisted of a weight per age lower than 70% in absence of edema. The recruited group (6 treated infants and 3 control infants) was rather homogeneous also for the diagnosis that was of persistent diarrhea. Persisting diarrhea showed constant associations with high plasma triglycerides, with remission of diarrhea and a lowering of high plasma triglycerides after treatment by IHMP.^{25,27,52} These associations, remarkably high triglycerides, are consistent with a state of insulin resistance at recruitment.^{53,54} Insulin resistance is associated with a high level energy balance both in blood and in the body,^{55,56} We found 15%-20% higher energy intake and higher energy expenditure above IHMP by doubly labeled water and indirect calorimetry.⁵² The energy balance kept at high level always implies an insulin resistance and fattening.²⁴⁻⁴¹ The fattening may be modest or conspicuous depending on insulin production.⁵² An energy balance kept at high levels is associated with an absorption slowdown [48-51,57,58] and long permanence of food on intestinal mucosa that promotes bacterial growth¹⁹ and diarrhea relapses.^{13,14,19} We have tentatively studied the

association between immunogenic bacteria (Not pathogenic E. coli) growth and low grade inflammation in the intestinal mucosa.^{59,60} We found an increase in lymphocytes, plasma cells and cellularity in the lamina propria and in the epithelium. An increase of the infiltration has been reported in association with insulin resistance and/or diarrhea persistence.^{38-41,61} In the sixties, a number of state prisoners volunteered an experiment on energy intake decrease for months. This experiment, called Minnesota experiment, found consistent results during refeeding.⁶² Maintaining fat stores in a state of depletion are likely to provide a stronger drive to eat in malnourished patients, and thereby promote rapid lean tissue recovery.⁶²

On these grounds, we may order the consecution of events in the investigated children. Pathogenesis: maximal food administration, energy balance at a high or maximal level (insulin resistance), slowdown of intestinal absorption, bacterial overgrowth in the small intestine, increase in immune stimulation by one or two bacteria species, overall subclinical inflammation^{7,10,32-41} and diarrhea. Recovery: adoption of IHMP, decrease in food permanence on mucosa, reduction or elimination of bacterial growth in small intestine, improvement in absorption and regression of mucosal inflammation and diarrhea as well. IHMP is thus mainly purposed to lower intestinal immune stimulation and the development of an overall inflammatory state.

Conclusion

The choice between scheduled and requested meals may be a historical or fashion issue. In the first days of life, the two choices are equivalent and are dictated by familial and physician customs, local current fashion, convenience. A null hypothesis between scheduled and demanded meals has been rejected by our studies in infants.^{25,52} Given the facts that,

- By free choice part of the population maintains preprandial low blood glucose like during IHMP.
- The shown maintenance of requested meals up to 12 years of age.
- The equivalence of early instructions for novel mothers.
- The habitual, persistent nature of mean BG due to associated organic changes, and emphasizing the better health in children and adults who maintain IHMP, we suggest that a change in instructions on rearing is obvious and mandatory from the neonatal days.

Final remark

Maintenance of an energy balance at a proper level is difficult and poorly explored. Our investigations on hunger add reproducible, psychic targets that can be learned to decrease balance and intake uncertainty. Teaching this scientific information may become widely credited if it comes from official statey institutions (University and School) and not from marketed enterprises.

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Conflicts of interest

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