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Research Article

Conditioned intake: is it safe?

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Abstract

We studied meal patterns, blood glucose (BG), and body weight in children, and added glucose tolerance tests (GTTs) in clinically healthy adults, to assess insulin sensitivity when presenting with functional disorders or overweight. By synchronous BG measurements, we taught patients to distinguish hunger sensations that are conditioned from those that arise after meal suspension. This pattern has been termed the Initial Hunger Meal Pattern (IHMP), to obtain meal-by-meal fasting nutrient levels (low BG) prior to the next meal, to suppress insulin resistance by this learned skill. In this report, we carefully considered many issues that have arisen by peers or circumstances. Considered altogether, the issues clarify the limits, the possibilities, and the effects of learning the correspondence between hunger sensations and BG. Ignoring these sensations may contribute to increase obesity and diabetes in children. Asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, schizophrenia have increased in the last half century. A new formulation of the National Children's Study (NCS) should focus on the current inability of people to recognize hunger in correlation with BG.

Keywords: Blood Glucose; Diabetes; Insulin Resistance; Overweight; Fattening; Energy Balance; Energy Intake; Hunger; Meal Onset; Energy Availability; Bowel disorders.

Introduction

Bacteria grow on the intestinal mucosa during meal absorption, and gastroenterology disorders might depend on this growth that arises when absorption slows down [1-5]. In turn, this slowdown depends on energy imbalance when the intake is larger than the expenditure [5-10]. We found that xylose absorption slows down when energy availability increases during periods of low expenditure [4-7]. Alimentary diabetes consists of a long persistence of this imbalance. Even before full diabetes development, insulin resistance is associated with an immune overstimulation variously termed: sterile inflammation, overall subclinical inflammation, proinflammatory state [11-23]. Intestinal disorders are a part of this state [11]. We tried to elevate the subjective awareness on current energy availability to the moment of energy intake. Conditioned hunger/intake is subjectively different from recognizing the hunger/intake that develops after meal suspension [24-36]. Conditioned hunger intake may allow intake before oxidative exhaustion of previous energy intake. To reject the null hypothesis between the two different intake ways, we assessed energy intake, blood glucose concentration (BG), insulin sensitivity, body weight, skinfold thickness, resting metabolic rate, total energy expenditure, cardiovascular risk factors, infection by Helicobacter pylori and persistence of functional bowel disorders in infants and in adults [24-27].

General Methods

During the forty-year-long activity of the Pediatric Gastroenterology Unit of Florence University, patients were divided by age and diagnosis at recruitment in prospective, randomized, controlled, cohort, necessarily not-blinded studies. children and adults had functional bowel disorders, and required diagnoses (Celiac disease) and treatments [24-27]. These patients received the same written instructions and the same assessments throughout the lab activity. Assessments consisted in: energy intake, blood glucose concentration (BG), insulin sensitivity

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byGGT, glycated hemoglobin, body weight, skinfold thickness, resting metabolic rate (RMR) by indirect calorimetry, total energy expenditure (TEE) by doubly labeled water, cardiovascular risk factors (total and HDL cholesterol, blood pressure), infection by H pylori, and persistence of bowel disorders [24-27]. An indispensable assessment consisted in checking compliance with IH arousal and low BG before any meal by phone calls and diaries [24-27]. Further details on recruitment, randomization, validations of food diaries and on BG pre-prandial measurements by portable instruments are reported in the research articles [24-27].

Blood glucose representativeness

Blood glucose has a central role in the regulation of energy metabolism. The Tuscan population consumes almost 60% of energy in the form of carbohydrates. Glucose provides energy to the brain, has limited and exhaustible storage and is regulated by the availability of other nutrients. Its blood levels are correlated with the time interval between spontaneously requested meals [28, 37-39]. Glucose (as well as proteins) is used before other nutrients and this utilization decreases when other nutrients are abundant [40-44]. Glucose does not stop its decline because reserves are exhaustible [44]. Fat calories are burned and stored several times slower than non-fat calories [40-44]. Changes in fat intake do not acutely affect fat oxidation but are matched by changes in storage [40]. We assumed that, blood glucose concentration (BG) was representative, as an index, of total energy availability for body tissues in the studied, clinically healthy subjects.

Validity of a portable device for BG measurements

We relied on objective measurements achieved through a hospital autoanalyzer to assess the difference between estimated and measured BG and we relied on the measurement of the RMR and on the measurement of the TEE to validate diary energy intake. Both BG and insulin measurements in adults were analyzed in our hospital lab by standard procedures. The compliance with training was however ascertained by home BG measurements before the three main meals, by a portable device (a portable potentiometer for whole BG measurement: Glucocard Memory; Menarini Diagnostics; Florence, Italy). We attempted to validate these BG measurements in many ways. At blood sampling in the lab, we supervised the performance of the comparison between the subject and the autoanalyzer. The autoanalyzer was checked every morning in comparison with the other 50 laboratories in Tuscany. A difference in BG from the mean had to remain within 1% every day. The heparinized blood sample for the autoanalyzer was immediately centrifuged and measured enzymatically. In the meantime, the patient performed his/her measurements on the same blood sample by glucometer. The autoanalyzer obtained a mean ± SD of 89.9 ± 11.3 mg/dL (N = 85). Subjects measured 89.0 ± 12.5 mg/dL. The mean difference (0.9 ± 7.1) was not significant. On absolute values, the mean difference was: 5.7 ± 4.3 mg/dL These mean differences imply no bias. In percentage, there was a mean 6.3% glucometer error of the autoanalyzer measurement. Subjects also calibrated their instruments 10 times on a standard 100 mg/dL glucose solution, and we tabulated over ten thousands of these calibrations. Overall, the calibrations confirmed the absence of biases and the validity of the BG measurements excluding variations over the years, although occasional derangements dissuaded their use for adjustment purposes of individual diaries.

Training protocol

1: Suspend meals for up to 48 hours

2: Locate physical sensation of hunger

3: Measure blood glucose concentration (BG)

4: Mentally associate the physical sensation with the BG concentration

5: Begin with a meal of about 300 kcal

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 appearance of physical hunger, compare the sensation and the measured BG with the previous sensations.

1On physiological and on microbiological grounds, hunger arousal might be the preferred moment for intake [1, 45]. The moment of food demand had to be well defined, to be recognized by all adults as well as by all mothers taking care of their children (reproducible). Initial Hunger (IH) emerged after meal suspension as a biophysical, subjective sensation that coincided with a recognizable (constant) physiological state of diminishing energy availability. The physiological state recurred some times per day and suggested spontaneously energy intake in absence of visual, smell or word food cues [24-27,30,31]. Blood glucose (BG) identified the energy availability at IH recognition.. In ten adults, hunger training appeared to be a feasible method and was successful in 84% of preprandial instances over two weeks, when an individualised fasting blood glucose was used to indicate that a meal can begin (See above the protocol) [46].

Reproducibility of IH recognition

The recognition of IH was reproducible in the same subject as well as in other subjects approximately at the same set point in BG, provided that they led a sedentary lifestyle. In table 1, we report final values in 27 adults (who remained at high mean BG) out of 89 who practiced IHMP for 5 months [34]. Six out of 27 were engaged in heavy manual work in an open air cold climate. They asserted to comply accurately with IHMP and high insulin sensitivity supported their reports. Heavy physical activity may require high BG and impose IH arousal when BG is high for sedentary people.

Adjusting energy intake according to hunger sensations to

	6 HBGa	21 HBGb
Final Mean blood glucose (mg/dL)	86.4 ± 4.0	87.1 ± 5.3
Final insulin AUC (mU L–13h–1)	124 ± 26	207 ± 99c
Final blood glucose AUC (mg dL–13h–1)	536 ± 56	601 ± 82d
Insulin sensitivity index	11.4 ± 2.9	6.68 ± 4.0e
Beta cell function index	1.29 ± 0.66	1.43 ± 1.22

Table 1: Effects of heavy outdoor work in 6 out of 27 trained subjects who remained with high BG at investigation end [34]. (Courtesy of the Authors [34]).

Notes: aSix HBG subjects reported doing heavy work all day in outdoor environment during cold weather while practicing "recognizing hunger". No significant differences in the five parameters from recruitment. At recruitment, mean BG = 86.9 ± 5.3 mg/dL in 27 HBG subjects; bThe 21 HBG subjects included 15 that were LBG after 7 weeks training (clinical assessment) and six who had higher mean BG than 100 mg/dL at recruitment; cP , 0.01; dP , 0.05; eP , 0.001.

maintain steady, optimal blood glucose (energy availability).

The treatment consisted in a meal by meal exhaustion of nutrients added to blood with the last meals to prevent absorption slowdowns and to avoid diarrhea relapses. In the first decade of our studies in a pediatric ward, we did not measure BG before meals and we limited children's intake by administering food only after demand (See also Birch) [30]. We never implemented a biochemical limit [24-27]. In the occurrence of a discrepancy (hunger arousal and high BG), we suggested mothers (and adults for themselves) to allow child's manifestations to prevail (IH arousal and IHMP). The infant did not suffer hunger endurance, its intake had a limit and the limit was easily recognizable [24-27,31]

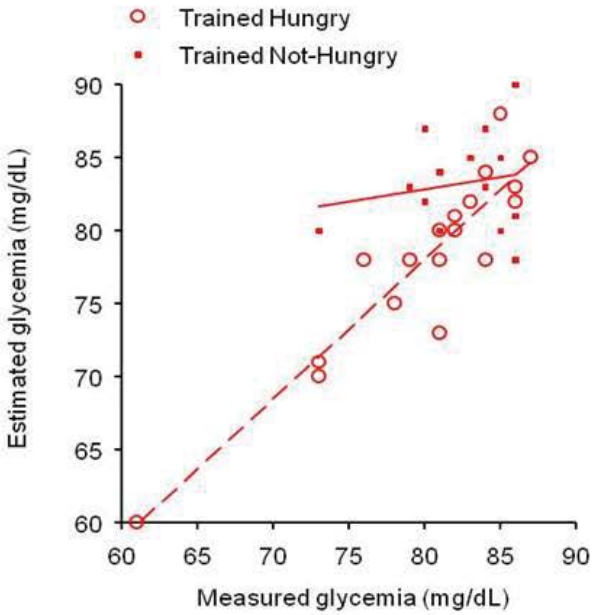

Figure 1: Estimated vs measured blood glucose of trained subjects with levels below 87 mg/dL at the final session.

Notes: The highest glycemic value measured in trained hungry subjects was 87 mg/dL. Below this value of measured blood glucose, 18 subjects reported to be hungry (hollow red circles) and 14 subjects were not hungry (filled red squares). Linear regression is significant for the hungry subjects (dashed red line; r = 0.92; p = 0.0001) but not for those not hungry (solid red line; r = 0.18; p = 0.54). (Courtesy of the Authors [31]).

Validation of diary energy intake decrease by measurement of RMR and TEE

OW people had the only imposition to evaluate approximately meal intake to prevent hunger arousal before the planned subsequent intake. We measured body weight at start and end of the 7 day diary and the body weight decrease of some kg suggested a underreporting (no representativeness) in OW people who wanted a weight decrease. We found no underreporting in diaries of infant/mother pairs who wanted a treatment for bowel disorders [26]. We studied 24 infants with functional disorders of the bowel with regard to: a) energy intake by a 10-day food diary; b) RMR (indirect calorimetry) in 14 toddlers; and c) TEE by doubly labeled water in 10 toddlers [26]. Their blood parameters, anthropometry, and number of days with diarrhea were assessed before training and 50 days after training. Energy intake decreased from 85.7 ± 15.3 to 70.3 ± 15.8 kcal/kg/d (–17.9%; P < 0.001). and TEE decreased from 80.1 ± 6.9 to 67.8 ± 10.0 kcal/kg/d (-15.5%; P < 0.001). We found no statistical difference between intake and expenditure at recruitment, after training and in the decrease that occurred after recruitment. Intake decreased more (the difference was not significant) than expenditure, but also fecal energy loss decreased during IHMP compensating the modest intake decrease [47]. RMR decreased from 58.6 ± 7.8 to 49.0 ± 9.1 kcal/kg/d (-15.4%; P < 0.001). The height Z-score increased significantly, while weight growth was normal. All studies on energy intake, TEE, RMR, and BG in infants reject the null hypothesis between the trained condition (during IHMP) and the untrained condition.

Mind and body weaknesses

All over the world, the word hunger indicates gastric sensations of emptiness or gastric pangs. Mind and body weakness might promote or suggest intake. During weakness hunger, BG, BG estimation error and RMR have low values [26, 31, 48]. These characteristics suggest that weakness hunger is a reliable signal for intake just like hunger pangs. In the not-hungry subjects' reports, sensations of mental weakness consisted of difficulty in sustained mental concentration, impatience, irritability, drowsiness, gnawing sensations, loss of enthusiasm and effectiveness at mental work, or poor mood at work. Moreover mental sensations emerged alone or in addition to gastric or other sensations and ceased with the meal. Sensing impairment during physical activity was associated with heavy physical exercise outdoors and often it went on with a

change from a sedentary lifestyle. These sensations were regularly used to indicate a meal signal. The prevalence of these "hunger equivalents" ranged from an occasional occurrence to about 15% of all meals reported by phone [33]. Two subjects reported that they never felt gastric hunger, but estimated BG within 6% estimation error always by assessing mental or muscular weakness during training or during the final investigative session. Thus, trained subjects are able to recognize hunger by gastric sensations or by body or mental weakness. The first signal is a threshold and is quite definite. The second is gradual and unspecific. Mind weakness is more frequent than body weakness. Also Caudwell found weakness and low RMR as signals for starting meals [48]. We asked a lean adult (BMI = 20). to endure body weakness until his BG reached 80 mg/dL. He did not feel any more gastric hunger before meals but ate at low BG, about 80 mg/dL, and lost 7 kg body weight in 40 days. The subsequent instructions, consuming meals as soon as he felt weak, increased pre-prandial BG to 85 mg/dL and let him recover 3.5 kg. [34]

Distinguishing conditioned hunger from hunger after meal suspension (IH Validation)

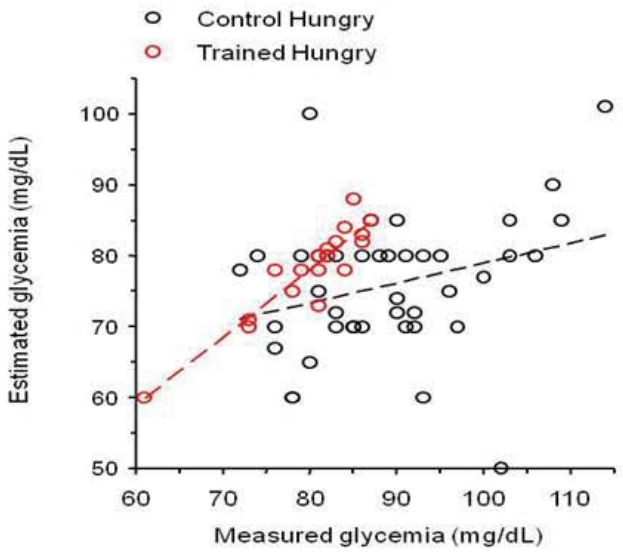

Figure 2: Estimated vs measured blood glucose of subjects reporting to be hungry at the final laboratory investigative session. (Courtesy of the Authors [31]).

Notes: Hollow red circles, trained hungry subjects (n = 18); hollow black circles, control (untrained) hungry subjects (n = 42).

Linear correlation was significant for the trained data (dashed red line; r = 0.92; p = 0.0001) but not for the control data (dashed black line; r = 0.29, p = 0.06).

Humans recognize sounds and colors. Do adults similarly learn to recognize gastric sensations of hunger that arise after meal suspension from conditioned hunger sensations? We studied this occurrence in adults who were less than 60 years old. The training consisted in BG measurements at hunger arousal, lasted two weeks, and one month later 64 trained and 72 control subjects came to the hospital lab before breakfast following an overnight fasting.31-33 All subjects declared current presence or absence of hunger, and estimated BG. A glucose autoanalyzer measured actual BG. The number of control subjects (42 out of 72) stating hunger was significantly higher than the number of hungry trained subjects (18 out of 64).31 All hungry subjects described hunger sensations as gastric emptiness or gastric pangs. In the hungry trained group, the mean estimated BG was 78.1 ± 6.7 and the mean measured value was 80.1 ± 6.3 mg/dL This measured BG was significantly lower than the measurements in hungry control subjects (89.2 ± 10.2 mg/dL) and in not-hungry subjects of both trained (90.0 ± 6.6 mg/dL) and control (90.6 ± 10.9 mg/dL) groups. The absolute value of the difference between estimated and measured glucose (estimation error) in the hungry trained group (3.2 ± 2.4% of the measured value) was significantly lower than the one in the hungry control group (16.7 ± 11.0%). Linear regressions of the values in the hungry groups show that there was a significant correlation between estimated and measured BG in the trained group (r = 0.92; P= 0.0001) but not in the control group (r = 0.29; P= 0.06). All these findings prove that control (untrained) subjects do not reflect their biochemical condition when stating to be hungry and estimating BG. Trained subjects instead, show a low BG condition when hungry and estimate accurately their current energy availability.

Differences between conditioned hunger and hunger after meal suspension

In the hospital lab, subjects asserted their BG and hunger state some minutes before they were free to have breakfast. Right after the question on hunger, control subjects focused on food and developed gastroduodenal Pavlovian reflexes. They described hunger as a tenuous, continuous state of hollow stomach rather than intermittent sensations of wave bursts as physiological studies suggest. Their statements reflected a lack of habit to self-observation and a lack of the habit to compare current sensations to past experiences. Humans tend to maintain constant BG before meals (confidence interval ± 3.8 mg/dL around mean BG in a week. See later). Control subjects who asserted to be hungry, did not get out of their personal, habitual high BG level.34 Only a minority showed the value we found at the exhaustion of the previous meal (See Introduction).31-34 Except for this minority, control subjects reported conditioned hunger, a mere remembering of the physiological events that characterize hunger after meal suspension. All these differences are modest, the main difference is at the onset: either before focusing on food (after meal suspension) or after focusing on food (conditioned). Low BG can confirm this distinction.

Conditioned hunger and hunger after meal suspension, effects on BG and on energy intake in infants

In infants, we scientifically approached this difference

between the "conditioned" and the "after meal suspension" hungers by multiple studies [24-27]. In the hospital laboratory before breakfast, we investigated 16 toddlers not demanding food in comparison with 54 toddlers who were demanding food, all after training with 42 measurements at hunger arousal [25]. No demand was associated with a significantly higher BG than the condition of food demand (96.3 ± 10.5 mg/dL versus 74.6 ± 7.7 mg/dL; P = 0.0001). Based on these studies, the initial demand (ID or IH) was conceived as a threshold phenomenon triggered by low energy availability in blood, indicated by low BG;25,26,31 normal activity is not inhibited by low energy. The intervention may be conceived as an abrupt weaning of the child from the automatic, scheduled feeding to implement, with the mother, a habitual evaluation of the amount to be eaten. We compared 70 mother/infant pairs with 73 randomly selected untrained controls, using a 7-day food diary, anthropometry and blood examinations before training and 4 months after training. Energy intake remained stable in control children (from 968 ± 173 to 1148 ± 314 kcal/day). In trained mother/infant pairs, energy intake significantly decreased from 946 ± 230 to 749 ± 187 kcal/day (- 20.8%; P < 0.001). In the longitudinal comparison the decrease was significantly larger in the trained pairs than in control infants who maintained scheduled meals (P < 0.001). We found no difference in body weight growth and in skinfold thickness. This study demonstrated that IHMP is associated with a significantly lower intake and a similar growth in infants. This discrepancy opened a new problem: why a similar growth and a different energy intake?

Energy intake and acceleration in body weight growth

A positive, significant correlation has been shown between energy intake and acceleration in body weight growth but this correlation is not equally effective in all children [24]. Toddlers with chronic/recurrent diarrhea in the second year of life, develop diarrhea instead of fattening and accelerate growth when they increase intake with conditioned meal-pattern: they have significantly thinner skinfolds than the normal mean reference in association with significantly lower basal insulin up to the seventh year of life [49] Eighty-two out of 91 trained child/mother pairs and 32 out of 41 randomized pairs in the control group were followed up to four years. In the four years, the control group maintained a significantly higher energy intake (15% - 30%) compared to the trained group without any fattening or growth acceleration or any improved results in intermeal behavior, intellectual or physical achievements or blood parameters in the four years. A similar, controlled study on diarrheic, two year old infants was prolonged for a mean of ten years in 86 healthy infants on prevention of Helicobacter pylori infection.23 Seven-day home diaries reported mean pre-prandial BG, daily intakes, activity and bedtime hours. Mean BG were 90.0 ± 5.4 mg/dL and 82.8 ± 10.8 mg/dL in the control and trained children at the age of twelve (P < 0.05). Daily energy intake (kcal/day) were 1527 ± 478 and 1228 ± 419 (P < 0.01). The Increase in body weight per height were 10.3 ± 13.7 % and 3.1 ± 12.5 % of the median body weight US reference for the same age (P < 0.05). We concluded that toddlers with chronic non-specific diarrhea have poor fattening capability for inborn, hormonal factors, including low basal insulin. In the general population, this may mean that there are wide inter-individual differences in fattening capabilities.

Findings in "Undernourished" Infants

In our diagnosis and treatment we encountered infants with malabsorption who were not celiac.50 We assigned them to either intervention or control feeding and trained the intervention group by IHMP. We intended to suppress the HBG state and achieve recovery. The data from 9 diarrheic, malnourished infants under 15 months of age, a weight per age lower than 70% and chronic diarrhea, were available for the first two years of follow-up [50]. Six subjects (age 2 – 14 months) under intervention were compared to three control subjects (age 2 – 14 months), who were conventionally fed at scheduled mealtimes. Organic diseases were excluded by conventional procedures, including intestinal biopsy. Compliance, intake, and anthropometry were recorded in hospital for 2 months, and then by frequent visiting and 7-day home diary for 5 total times in two years. Energy intake, anthropometric measurements and blood tests, school performances, and symptom prevalence showed functional and nutritional outcomes (Figures 3 and 4) [50].

Energy intake decreased from 111 ± 53 kcal/kg/d to 107 ± 37 kcal/kg/d in control subjects and from 126 ± 21 kcal/kg/d to 85 ± 6 kcal/kg/d in treated infants in the first 2 months of study (P < 0.01 on longitudinal differences). Four or five days with vomiting in 60

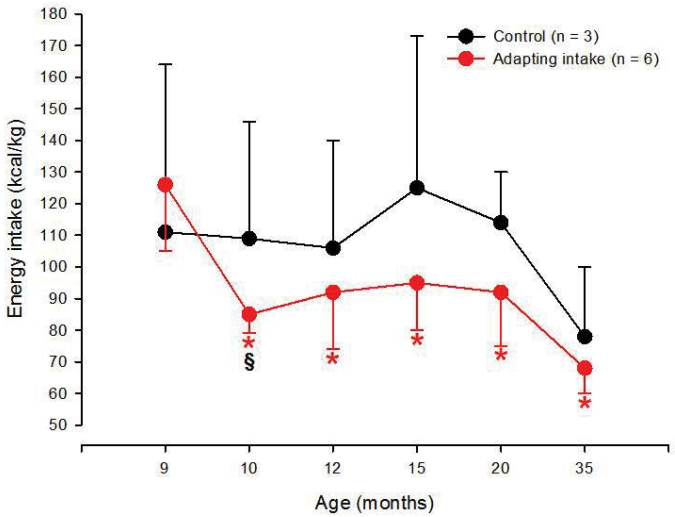

Figure 3: Daily energy intake in treated (6, black circles) and control (3, Red circles) subjects during two follow-up years. (Courtesy of the Authors [50]).

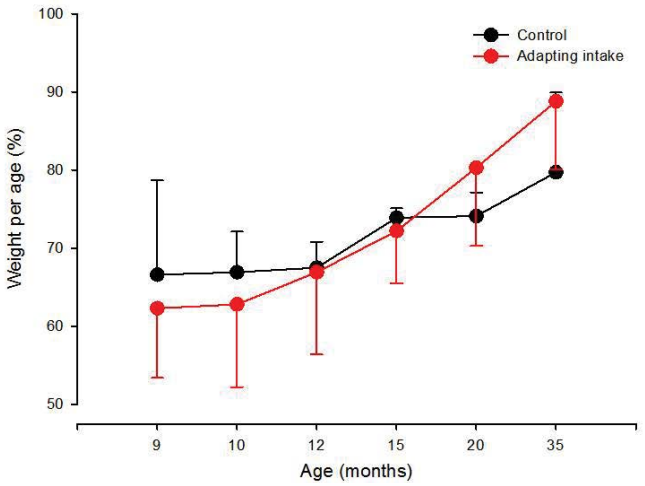

Figure 4: Growth of body weight in 6 treated and 3 control malnourished infants from a mean age of 9 to 35 months of age. (Courtesy of the Authors [50]).

days persisted in control subjects for all follow-ups, but became null after 2 months of treatment. Further longitudinal differences were significant on days with diarrhea after three months, and on plasma triglycerides at the two sampled times during treatment. These assessments were all significant by Chi square for trend during the follow-up ($P < 0.01$). 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 a 2-year follow-up were respectively: 73.2 ± 12.3 mg/dL and 89 ± 37 mg/dL ($P < 0.05$). Toward the end of the study, anthropometric measurements in treated infants increased per age from recruitment. The differences from control subjects that were not significant in each of the five assessments during the follow-up were significant by Chi square for trend (Figures 3 and 4). After two years, weight per age reached 88.8 ± 8.7% under intervention and 79.7 ± 10.2% in controls ($P < 0.01$ by Chi square for trend). Psycho-motor development was normal, except for one control infant. To conclude, in these undernourished infants, high triglycerides and insulin resistance are involved in the development of persistent diarrhea, overall subclinical inflammation and malnutrition.

Findings in the second year of life

In the year 1990, we published findings in 44 infants under IHMP in comparison with 44 control infants [24]. All subjects had chronic non-specific diarrhea. In the trained group, energy intake decreased significantly by almost one third. Growth, skinfold thickness measurements and outdoor activities were similar between experimental and control groups over a 7-month period. During the 7-month period, diarrheal episodes persisted in the control group. The difference between the control group and the trained group was significant ($P < 0.002$). At final examination, we compared the mean values of 32 parameters of clinical status in the two groups: twenty parameters had clinically improved in the trained group and 9 parameters had improved in the control group ($P < 0.05$). We considered this difference insufficient to show a better global outcome, but trained mothers were happy of the results. In addition to energy intake decrease, the experimental group decreased significantly the mean weekly pre-prandial BG from 81.7 ± 13.6 mg/dL at baseline to 71.6 ± 9.3 /dL after 7 months of IHMP. Plasma triglycerides significantly decreased during IHMP from 83.2 ± 35.8 to 64.4 ± 18.8 mg/dL ($P < 0.01$) in 24 toddlers [26]. Mean blood glucose decreased from 86.9 ± 9.4 mg/dL to 76.4 ± 6.7 mg/dL in 70 infants in a controlled study in comparison with 73 control infants ($P < 0.0001$),25 IHMP had similar results in all other studies.

Adult Investigations

Between 1995 and 2000, OW subjects with functional bowel disorders came to the University Pediatric Gastroenterology Unit for diagnostic purposes, mainly Celiac disease, and for treatment. A total of 181 subjects aged between 18 and 60, clinically healthy, were recruited for a treatment by IHMP. We randomly assigned all subjects to controlled studies in which the primary outcome was weight.32,33 One-hundred and forty-nine subjects completed the study on body weight and 120 subjects completed a second study where the primary outcome was insulin sensitivity [34,35]. Sixty-six NW subjects and 38 OW subjects were trained in IHMP over a 7-week period and were after followed for further 3 months. Twenty-four NW and 21 OW subjects formed the control groups [32].

Mean blood glucose: IHMP and HBG

The accurate definition of Initial Hunger allowed the construction of a new dietary lifestyle: the Initial Hunger Meal pattern (IHMP), dictated by the rhythmic arousal of Initial Hunger three times a day. A meal usually follows the IH arousal. The subject requires information on energy content of food and on factors of energy expenditure in addition to IH recognition. We directed these adjustments by phone. Subjects kept food home week diaries at recruitment, after two, three, and five months and afterwards yearly. This diary offers an unprecedented insight on energy availability in all tissues with the BG measurements. "Mean BG" is the mean of 21 measurements in the quarter-of-an-hour before the three main meals reported by week diaries. The series of BG measurements before meals (summarized in Mean BG) have the advantage of being comparable with subsequent times after months and years as well as being comparable with other subjects. At recruitment, BG wavered ±3.8 mg/dL (confidence interval around the mean) in 120 week-diaries [34]. In the same 120 adults, Mean BG could be stratified in ten strata. Each stratum contained subjects who showed no significant Mean BG difference compared to other subjects in the same stratum, but had a significantly different Mean BG compared to other strata. In 31

control subjects, Mean BG was 85.2 ± 8.1 mg/dL and 85.3 ± 7.6 mg/dL after 5 months [34]. The absolute pre/post change (increase or decrease) was 6.0 ± 4.6 mg/dL. With these characteristics, the biochemical and biophysical background before meals is rather constant in the single individual even if conditioned. However, the mean preprandial BG before meals differs from one individual to another, 34 and the differences are maintained as habits. Mean BG measures the level of energy balance in blood, even more important, it shows energy availability in tissues (and in afferent terminals), is stable, personal, stratified and in closer relation to the insulin area under curve (AUC, r = 0.45) during GGT compared to body weight (r = 0.06). Mean BG might be the principal factor for the development of feedback pathogenic reactions that are associated with insulin resistance. Mean BG, as a stable pre-prandial level, assesses the distance of the habitual meal pattern from two opposite extremes in the energy balance: energy insufficiency and insulin resistance. Moreover it assesses the deviation of the individual meal pattern from the Mean BG associated with IHMP) [34]. This assessment is useful to check compliance with the training. The association between Mean BG and insulin resistance implies that risks and illnesses associated with Insulin resistance are also associated with Mean BG. The stratification by Mean BG is directly associated with insulin resistance and vascular risks and is similar (in correlation) to the stratification between glycated hemoglobin and vascular hazard ratios [34,51,52] These associations are strong and independent on our microflora studies.1

Initial Hunger Meal Pattern (IHMP) and Insulin sensitivity

IHMP implementation significantly decreases insulin and BG peaks, decreases insulin at 60 minutes and 90 minutes during the GTT, glycated hemoglobin, Mean BG, energy intake and BMI when compared to controls. The insulin sensitivity index increases from 7.1 ± 4.1 to 9.4 ± 5.2. The increase is significant in comparison with controls (P < 0.01) and in comparison with baseline values (P < 0.001) [35, 53]

HBG at recruitment and decrease during IHMP: a correlation (Table 2).

We noticed that, at recruitment, Mean BG ranged from 64.5 mg/dL to 109.9 mg/dL [35]. This wide distribution suggested that, the overall improvement in insulin sensitivity could be mostly explained by the improvements in subjects whose Mean BG was high at recruitment. Furthermore, we have already found that at recruitment the mean confidence interval (95%) around the Mean BG was only ± 3.84 mg/dL (See above). Thus, although subjects differed widely from one another in Mean BG, their own individual pre-meal BG concentration varied little during the diary week. This suggests that many people eat in a conditioned style, irrespective

	Low BG group				High BG group			
	Control		Trained		Control		Trained	
	Recruitment	After 5 mo.	Recruitment	After 5 mo.	Recruitment	After 5 mo.	Recruitment	After 5 mo.
Mean pre-meal BG (mg/dL)	76.9±3.[4]	79.1±3.5	76.6±3.7	77.2±4.2	90.4±5.3	89.2±6.9	91.6±7.7***,c	81.0±7.7 ***,a ***,b
BG diary SD (mg/dL) [1]	7.6±2.3	8.7±1.7**b	6.8±3.0	5.4±2.3 *,a **,b	9.0±3.3	9.3±3.9	9.4±4.8**,c	6.6±2.6**,a ***,b
Glycated Hb (%)	4.38±0.29	4.53±0.35	4.50±0.30	4.43±0.31	4.65±0.38	4.83±0.39	4.81±0.44***,c	4.56±0.47 ***,a ***,b
Insulin AUC[2] (mU $L^{-1}3h^{-1}$)	192±106	243±133	180±98	183±83*,a	222±81	215±98	244±138*,c	164±92**,a ***,b
Insulin peak (mU L^{-1})	66±30	83±41	62±44	58±30	75±33	68±36	79±46**,c	54±29*,a ***,b
Insulin sens. (index)[3]	14.6±7.2	11.8±5.8	15.9±8.3	15.7±9.0	6,0±2.2	6,8 ± 3,9	5.9±3.3***,c	9.8±5.6**,a ***,b
Insulingenic index [4]	0.9 ±0.6	0.8±0.6	0.9±0.9	1.0±0.7	1.1±1.2	0.7±0.7	1.0±0.7	1.4±1.1*a *,b
BG AUC (mg/dL)	547±117	542±126	548±73	537±81	627±101	598±107	639±98***,c	567±91***,b
BG peak (mg/dL)	124±25	124±30	119±22	122±24	136±22	128±27	145±27***,c	128±27***,b
Energy intake (kcal/d)	1803±567	1565±677	1568±612	1303±590***,b	1887±599	1703±557	1872±655*,c	1251±470 ***,a ***,b
Meals per day[5]	3.7±0.7	3.8±0.6	3.8±0.6	3.5±0.5**,b	4.0±0.7	3.9±0.7	3.9±0.7	3.7±0.7***,b
Vegetable intake (g/d)	272±265	292±223	388±257	492±217*,b	127±128	166±218	287±223*,c	392±251**,b
Fruit intake (g/d)	183±177	188±205	233±152	334±315	183±133	147±113	214±150	290±219*,a *,b

Table 2: Effects of training on metabolic and intake parameters in low and high BG subjects.

1 Diary SD refers to the mean of the mean BG standard deviations of 21 measurements reported by each of 7d diary.
2 AUC = area under GTT curve.
3 Whole body insulin sensitivity index.54
4 Insulinogenic index of beta cell function.55
5 Meal had an intake over 20 kcal.
Values are expressed as mean ± SD. Peak values
include different observations from those at 30' during GTT. Asterisks indicate a significant difference (Student's t-test: *, P < 0.05; **, P < 0.01; ***, P < 0.001) on pre/post difference vs.
Respective control group (a), or vs. the value of the same group at recruitment (b), or vs. the value of LBG trained group at recruitment (c).

of homeostasis and more likely associated with habits and with an increased number of beta cells in the pancreas. Other subjects ate at low BG concentration and thus probably already eating more or less according to homeostasis. To test this, the effect of IHMP was analyzed in both subgroups: those who were found to eat habitually at a HBG at recruitment and those who habitually ate at a LBG concentration at recruitment. The line of demarcation that divided the two groups was a Mean BG of 81.8 mg/dL (4.54 mmol/L). This was the BG value that statistically divided the most significantly the two groups. We performed the statistical analysis on the number of subjects who significantly decreased mean BG after training.

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IHMP and LBG group (Table 2).

Only 3 out of 34 trained subjects who had Mean BG lower than 81.8 mg/dL decreased significantly. Mean BG, whereas 41 out of 55 subjects, whose Mean BG was higher than 81.8 mg/dL significantly decreased Mean BG after training ($P < 0.0001$). At recruitment, the LBG subgroup showed significantly lower insulin, lower BG area under curve (AUC) in the oral glucose tolerance test (GTT), and lower HbA1c than the HBG group. Among LBG trained subjects (n = 34) Mean BG remained constant (pre: 76.6 ± 3.7 mg/dL; post: 77.2 ± 4.2 mg/dL; $P = 0.499$), as well as body weight, skinfold thickness, energy intake, insulin area under the curve, glycated hemoglobin and the index of whole body insulin sensitivity. Thus, a LBG group existed independently from any treatment. Their low Mean BG was optimal, homeostatic, physiologically appropriate for both energy needs and to prevent immune overstimulation [34].

At recruitment, i.e. in control groups as well as in subjects before training, we found a minority that had an LBG and showed a low error of estimation [25,26, 31-34]. The low estimation error demonstrates that these minorities may identify a sensation coincident with IH as a reference for eating in absence of any training. Given this presence of these minorities in all studies, and the attainment of similar BG at the end of GGTs of the homeostatic group [35], as well as the association with insulin sensitivity, IH may represent a physiological signal that was developed in the phylogeny to guide energy balance to the best survival. Initial Hunger (IH) corresponded precisely to this value in separate studies on mean weekly BG obtained by home diaries [25, 26, 31-34].

IHMP and HBG group.34

After training, HBG subjects significantly decreased their Mean BG (n = 55; pre: 91.6 ± 7.7 mg/dL; post: 81.0 ± 7.7 mg/dL; $P < 0.0001$; (Figure 5).

HBG trained subjects (but not LBG trained subjects) showed a cumulative energy balance that was negative through the 5 months of the study as indicated by measurements of skin-fold thickness. Trained HBG subjects, but not LBG subjects, showed a decreased insulin area under the curve, a decreased glycated hemoglobin, an increased index of whole body insulin sensitivity and an insulinogenic index. [34,52,54,55] Insulin production decreases with increasing duration of non-insulin dependent diabetes (NIDD) and HbA1c level.55 In this study, the High BG control subgroup decreased insulinogenic index of beta2 cell function, whereas the High BG trained subgroup increased it. The differences between control and trained subgroups were significant; this implies a higher insulin production, a preservation of the beta cell function, and the possibility of an innovative therapy aimed to preserve, or even improve, functional beta cell mass by IHMP.55

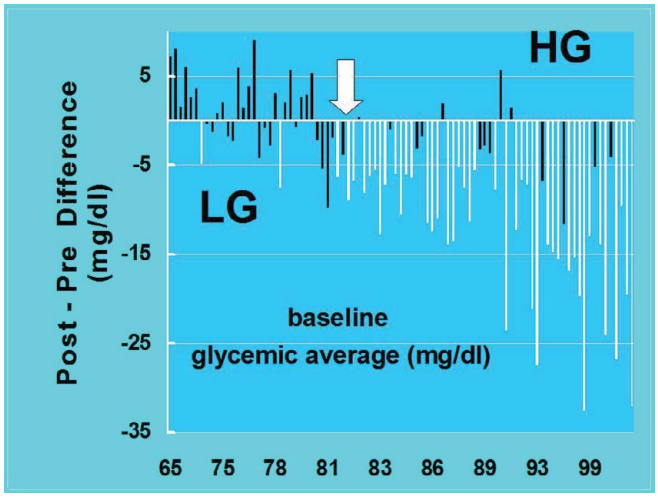

Figure 5: Difference of mean pre-prandial BG after training versus BG at recruitment for each trained subject.

Notes: Column height shows 5 months after pretraining mean BG difference in each trained subject. Significant increases are indicated by blue bars, significant decreases by red bars, and not significant changes by black bars. Mean BG is reported in sequentially increasing order at recruitment, not in linear correlation with segment length on the X-axis scale. The range of mean blood glucose values at recruitment is between 65 and 109 mg/dL.The vertical dashed line indicates the most significant division between subjects who showed no mean BG decrease after training (low BG group, n = 34) and those who showed significant decrease of mean BG (high BG group, n = 55; Chi-squared analysis: $P = 0.00001$). This threshold blood glucose at recruitment (demarcation point) is 81.8 mg/dL (4.54 mmol/L). Subjects above this threshold accounted for most of the improvements in weight and insulin resistance.32,34

Abbreviations: BG, blood glucose; HBG, high blood glucose; LBG, low blood glucose.

In a longitudinal investigation of 13,163 subjects, a fasting plasma glucose of 87 mg/dL (4.8 mmol/L) or higher, predicted an increased risk of NIDD in men compared with those whose fasting plasma glucose was 81 mg/dL (4.5 mmol/L) or lower [53].

Initial Hunger Meal Pattern (IHMP) and Body Weight

In trained OW subjects, body weight and BMI decreased after 7 weeks of training and after 3 further In trained OW subjects, body weight and BMI trained OW subjects, body weight and BMI decreased after 7 weeks of training and after 3 further months of IHMP implementation compared to controls.32 BMI decreased from 28.7 ± 3.5 to 26.5 ± 3.5 in the trained group, and the decrease was significant in comparison with controls (P = 0.004) and in comparison with the baseline values of the same group (P = 0.0001). Mean BG and training emerged as the most significant predictors of variations in BMI and body weight by multivariate analysis of variance.32 Also NW trained subjects, whose Mean BG was high at recruitment, lost weight compared to controls.32

Differences in weight loss between trained LBG and HBG subjects

A relation may exist between Mean BG and body weight.32 In post hoc analysis of our study on weight, subjects were divided into four groups according to weight (OW; NW) based on BMI and Mean BG at recruitment. The four groups were thus: OW HBG, OW LBG, NW HBG, and NW LBG. After training, OW HBG and OW LBG subjects lost weight and NW LBG subjects retained weight, further confirming the homeostatic nature of IHMP. However, also NW HBG subjects lost weight. The distinction between NW and OW based on BMI is, after all, arbitrary. Subjects with high Mean BG but "NW" have presumably endured energy imbalance and fat accumulation for less time than OW subjects. For this situation, we suggest the term "hidden fattening".

Discussion

Hunger is subjective but its BG background can be measured, compared, improved, recognized and learned as a limit in intake. Energy intake may be regulated in three or four meals in a day to have three or four hunger episodes during the day. A subjective awareness may dominate the energy balance. Some AA. are confirming this statement.30,46,48,56-59 At recruitment, the energy imbalance had a causal relation with fattening/insulin resistance, diarrheic relapses and the associated immune overstimulation recently termed sterile inflammation.10-23 This immune overstimulation may have a causal relation with the other illnesses that increased their prevalence in children in the previous half century: asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, schizophrenia in addition to obesity and diabetes [59,60].

In the first days of life, the two choices (either scheduled or demanded meals) are equivalent and are dictated by familial and physician's customs, by local current fashion, by convenience. Our studies in infants reject the null hypothesis between scheduled and demanded meals. We propose a new formulation of the National Children's Study (NCS) focusing on comparing the risks (vascular events, ADHD, Autism, malnutrition, etc.) between the two different food administrations, either scheduled or on demand, considering 1) that by free choice part of the population maintains pre-prandial low BG like during IHMP, 2) the shown maintenance of a meal pattern on demand up to 12 years of age,23,49 3) the equivalence of both instructions for novel mothers, 4) the habitual, persistent nature of mean weekly BG due to associated organic changes,34 5) the need for prevention of fattening/insulin resistance, overweight and associated risks [18, 56, 58, 59]11-23,32 and 6) emphasizing the cessation of intestinal disorders in children and adults who maintain IHMP, [24-27].

Conclusion

An overwhelming amount of published paper demonstrate that conditioned intake sustains fattening, insulin resistance and the associated immune depression (sterile inflammation). The optimal intake corresponded to a fixed LBG level before meals (76.6 ± 3.7 mg/dL for sedentary people) that can be easily maintained after learning the correspondence between sensations and BG before meals (Initial Hunger). A consistent minority maintains the LBG level by free choice, before any training in IHMP.

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Abbreviations: AUC, area under curve at glucose tolerance test; BG, blood glucose; HBG, high blood glucose (> 81.8 mg/dL); LBG, low blood glucose (<81.8 mg/dL) .Courtesy of M Ciampolini.35

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