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Initial Hunger, A Subjective, Reproducible Limit in Intake Associated with Low Blood Glucose (76.6±3.7 mg/dL): A Training for Malnourished Infants and Overweight Adults

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Abstract

Many infants suffer with malnutrition or relapsing diarrhea and the University Pediatric Gastroenterology Unit was committed in Florence to their treatment. These disorders are associated with conditioned meals, insulin resistance, 20% higher energy intake and 20% higher blood glucose (BG). The Unit had the chance of performing the first diagnoses of celiac disease in Tuscany and recruited adults with bowel disorders to check meal patterns in them. In this review, is described the training of the passage from scheduled to demanded meals in infants and in adults and the null hypothesis is tested on the difference. Energy intake was assessed by diaries and validated against Total Energy Expenditure by doubly labeled water. Reduction in energy intake was obtained by subjectively abolishing conditioned meals and by administering food only after demand by the infant or after hunger perception by the adult (Initial Hunger Meal Pattern or IHMP). BG (76.6±3.7 mg/dL) identified the metabolic background of the hunger sensation that allowed meal energy intake. During a week, the confidence interval of 21 measurements around the mean was 3.8 mg/dL and we used the mean value from 21 preprandial measurements (Mean BG, MBG) to assess and compare meal patterns and compare compliance with IHMP. Conditioned meals were those scheduled and/or presented to the infant as well to the adult by sight, smell, mentioning, gesturing or simply at a fixed mealtime. As regards intake, common wisdom considers conditioned meals as equivalent in the energy content to those demanded by an infant (null hypothesis) or after meal suspension and arousal of hunger in adults.

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The training consisted of meal suspension and of feeding after the first infant's demand or after an adult's self-noticing arousal of hunger (Initial Hunger Meal Pattern, IHMP). IHMP was checked by MBG and resulted to be associated with a significant decrease in diary-energy-intake, in preprandial blood glucose, in glycated hemoglobin, in body weight, in insulin AUC at glucose tolerance tests and in days with diarrhea as compared to randomized control subjects, who maintained conditioned meals, often scheduled. The individual regression toward an even energy balance was proportionate to the BG height at recruitment. Only two out of 21 trained infants who had mean blood glucose lower than 81.2 mg/dL at recruitment showed a statistically significant decrease in mean blood glucose, whereas 36 out of 49 infants above this cutoff level showed a statistically significant decrease after training. Twenty-four similar diarrheic infants of the same age were trained to IHMP and the resting metabolic rate (RMR) was measured by indirect calorimetry in 14, and total energy expenditure (TEE) by doubly labeled water in 10 infants. RMR decreased by 15.4%; TEE decreased by 15.5%, from 80.1 ± 6.9 to 67.8 ± 10.0 kcal/kg/d. In the synchronous ten day food diaries, energy intake decreased by 17.9%, from 85.7±15.3 to 70.3±15.8 kcal/kg/d (pre/post $P<0.001$) after intervention. No difference was found between TEE and energy intake at recruitment, at final assessments and in the pre/post decreases. These findings also validated diary energy assessments. The height Z-score increased significantly, while weight growth was normal. Thus, the null hypothesis between conditioned and demanded (IHMP) meals is rejected. Although the metabolic differences between conditioned and demanded (IHMP) meals are impressive and seemingly difficult to be achieved, a third of the investigated subjects showed the low MBG value of 76.6±3.7 mg/Dl already at recruitment. Moreover, all reported that they adapted themselves to IHMP easily: "would I have known earlier". Lastly, this review describes technical characteristics like hunger equivalents, adjustments of energy intake to energy expenditure, deceptive BG measurements and characteristics that emerge in contrast with scheduled meals. The intention is to allow accurate reproduction to professionals as well as to simple readers in search for an even energy balance. The even energy balance is the prerequisite for an elimination of body overall inflammation, of functional disorders and for elimination of the progression toward diabetes, vascular diseases and malignancies.

Key words: Blood Glucose, Diabetes, Energy Balance, Hunger, Malnutrition.

1. Introduction

In the following text we describe our observations, projects and findings on diarrheic and/or undernourished infants with diarrhoea, some basic facts of the intestine, of the immune response and intestinal bacteria. The alimentary canal is exposed to a large amount of viable bacteria: about one-hundred trillions per gram of content. Many hundreds of species have no immune effect on the mucosa, but there are 5% to 15% of species that are capable of eliciting an antibody response and inducing inflammation [1-3]. These immunogenic species alone do not provoke a general illness, but the antigen-immune elimination process damages underlying tissues [1]. The number of immune cells in the small intestinal mucosa is impressively large. Half of the immune cells of the whole body are in the small intestine [4-5]. The absorption of nutrients from food is thus a competition between mucosa cells and bacteria [2-3]. Figure 1 well represents the bacterial environment in intestinal lumen. For feeding and preventing bacterial growth mothers had to provide energy dense food only when necessary i.e., food was not offered when the child was calm and happy. Intake of offered food proportionately reduced the efficiency of the immune response in the not demanding subject. As soon as the infant changed his/her mood, the mother gave a meal. Missing a meal reduced the bacteria concentration by one logrhythm [2]. The child had not to suffer hunger but only signaling it. This was an Initial Hunger Meal Pattern (IHMP). In an example by Helicobacter pylori, Figure 2 reports that during IHMP and associated low mean preprandial BG in a week (MBG), antibody response to Helicobacter pylori decreased, presumably for lower H pylori growth.

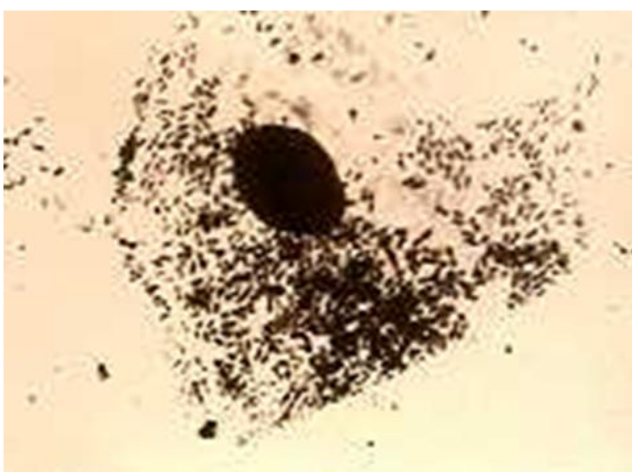

Figure 1. Epithelial cell shed from intestinal mucosa and covered by bacteria. Magnification is 2000X. (Courtesy of Ciampolini et al., 1996, [2] Copyright Clearance Center's Rights Link® service).

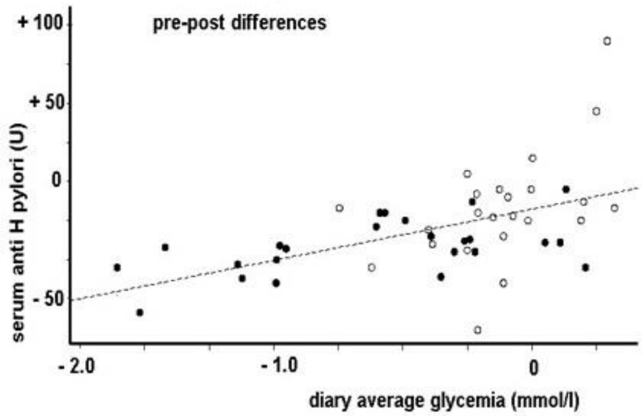

Figure 2. Positive correlation between serum concentration of anti-H. pylori and diary mean preprandial Blood Glucose (MBG). Values represent the pre/post differences. Black and white dots show trained and control subjects, respectively. n = 47, rho = 0.52, P < 0.0002. (Courtesy of Ciampolini et al., 2000 [3]; Copyright Clearance Center's Rights Link® service).

In our clinic we encountered most infants and adults with diarrhea and malabsorption who did not have Coeliac disease. We randomly assigned them to one of either two groups (i) intervention (IHMP), or (ii) control. Controls remained on conditioned feeding. There were thus two groups in comparison for infancy and two groups for adulthood. Groups of overweight adults and of malnourished infants provided further comparisons.

The intervention (Initial Hunger Meal Pattern, IHMP) consisted of suggesting subjects or mothers to suspend meals and to wait for the arousal of gastric pangs (adults) unexplainable unpleasant moods (infants), fussiness or walking in search for food or verbal orgestural demand for food before seeing the food or laid table [6].

The prevalent way of eating is conditioned and sets the limit (arbitrary!) on body weight or fatness [7-14], whereas IHMP sets the limit in the arousal of subjective hunger sensations. Conditioned meals are those suggested by sight or smell of food, by company, by laid table or by even mentioning these situations. Removing conditioned meals, i.e. implementing IHMP to achieve normative insulin sensitivity, abolished reflexes that depressed intestinal digestive functions as well as intestinal absorption [15-16]. A full achievement included elimination of insulin resistance and of the associated overall sterile inflammation [8]. In children, removing conditioned meals (i.e., implementing IHMP) decreased MBG and in adults decreased the area under curve (AUC) at Oral Glucose Tolerance tests (OGTTs) in association with lowering MBG [10, 17].

2. Investigating the portable glucose monitor

We investigated preprandial events in blood by week diaries that reported blood glucose measurements with a portable device before the three main meals. Single blood glucose measurements were performed with a reliable portable potentiometer using the hexokinase method (Glucocard Memory; Menarini diagnostics; Florence, Italy) at 15 minutes before each meal. The adults had to personally measure blood glucosein the same blood sample with the portable instrument. The reliability of the data was compared against the autoanalyzer results generated in the laboratory. The autoanalyzer obtained a mean ± SD of 89.9±11.3 mg/dL Adults measured 89.0±12.5 mg/dL (N=85). The mean difference (0.9±7.1) was not significant. On absolute values, the mean difference was: 5.7±4.3 mg/dL with no bias. Measurements from the blood glucose diary had a low confidence interval, 3.8 mg/dL that after 5 months was 6.0 mg/dL (no bias). Measuring preprandial blood glucose is directly useful for the patient who can directly notice previous unbalanced meals (between intake and expenditure) and so may make appropriate adjustments. Moreover he/she can learn the effects of physical exercise, open air, climate changes and occasional stressful and untoward events on blood glucose [6-7, 9-10, 17-18]. MBG characterizes the individual meal pattern better than energy intake and much better than single fasting measurements [10]. In the preprandial setting BG and MBG are directly associated with insulin resistance. BG summarizes the metabolic condition that follows the previous meal and shows the personal aim on energy availability [7, 9-10]. The metabolic condition created by previous meal ceases completely with the incoming meal. The glucose diary may be accurately performed by the patient under the surveillance of the family physician.

3. Standard measurement of blood glucose

Sampling BG after an overnight fast is poorly standardized. The liver delivers glucose into blood every 12 min resulting in approximately 10% changes [19]. Ambient temperature, physical activity, food and stress all significantly increase blood glucose. Half overweight (OW) subjects have high morning BG or do not consume breakfast and also those subjects who get breakfast have unpredictable fasting BG because of variability in time, energy amount and in composition of dinner and in activity, intake and time before going to bed and in insulation when in bed. Sampling blood glucose within 15 minutes before a meal is sufficiently reproducible (Confidence interval = 3.8 m/dL). BG measurement at this sampling summarizes energy availability and balance for the period from last meal to the moment of sampling, directly informing about either the abundance or insufficiency (energy balance) of the last meal in comparison with the expenditure between meals. The measurements at decision of receiving food energy indicates the aim for the energy availability (BG) for a given situation and individual. Being aware of this, was the best way to adjust meal energy; also overweight subjects lost their fear of hypoglycemic events later in the morning. Meal onset produces a completely new metabolic condition with an increase in energy availability for meal arrival, a change in metabolic rate and changes in gastric, intestinal, liver and pancreatic functions [15-16, 18].

The weekly MBG was calculated from 21 preprandial measurements in a week. MBG was consistent in a given subject because of the narrow confidence interval of preprandial BGs within the same person [10]. At recruitment, the BGs of 120 investigated adults by portable device showed a mean confidence interval of ±3.84 mg/dL at $P < 0.05$. By itself, this small confidence interval suggests reliability. The normal BG range between 65 and 110 mg/dL was obtained in our studies by measuring BG in different subjects. We could stratify the 120 subjects in ten small strata. Each stratum contained subjects without differences in MBG that instead were significant from all other strata. We might say that each subject maintained a meal pattern directed by the aim of a stable level of energy availability within his/her own MBG stratum even during ad libitum meal feeding, so that MBG represents also an intriguing assessment of the steps made in the pathogenic development toward diabetes. Infants' MBGs showed stratification in less strata. High energy availability is associated with depressed intestinal activity. To show the existence of this association, we reduced energy metabolic rate in the experimental animal and in humans by elevating environmental temperature and tested xylose absorption in experimental animals and humans in the two conditions of energy availability [High and low (Figure 3 & 4)].

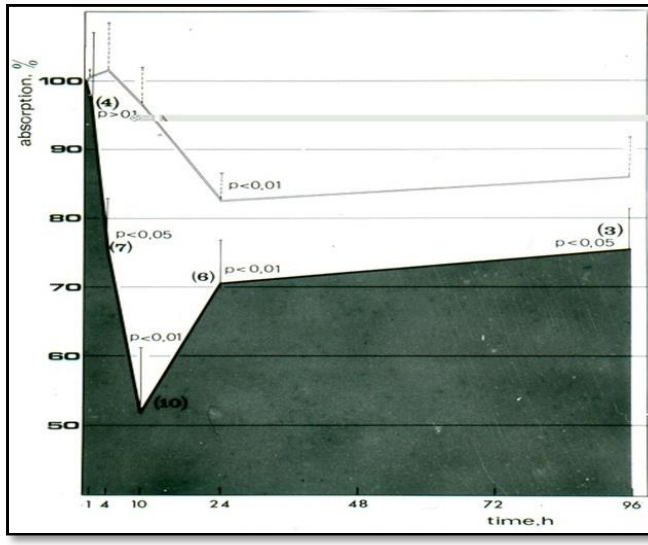

Figure 3. Percentage of increased absorption in cold environment (6 °C) over absorption in warm environment (31 °C) of intra-gastric xylose in rats. (Courtesy of Ciampolini, IRSC Journal of Medical Sciences 1974 [15], Copyright Clearance Center's Rights Link® service).

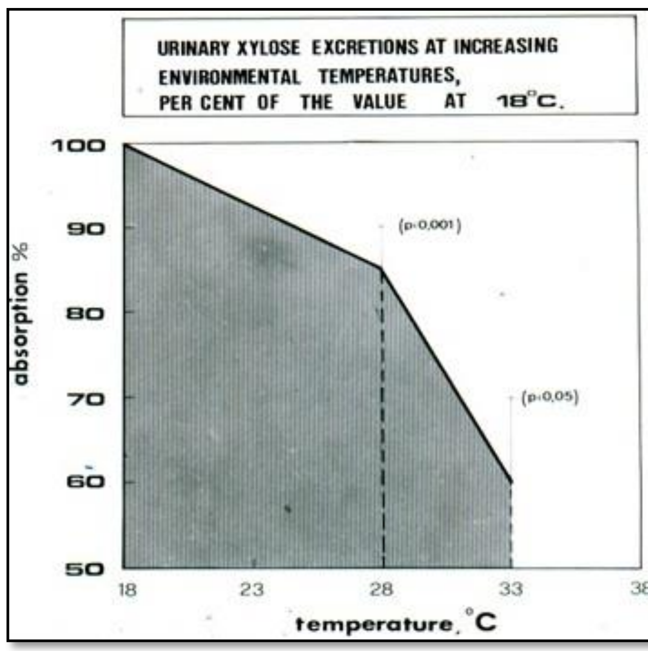

Figure 4. Significant, negative correlation between environmental temperature and xylose absorption in man. (Courtesy of Ciampolini, 1976 [16], Copyright Clearance Center's Rights Link® service.).

The high environmental temperature decreased intestinal absorption rate of xylose [15-16]. In this condition, long permanence of nutrients in the small intestine allows bacterial growth and possible diarrhea relapses. The relation between bacterial growth and diarrhea relapses has been separately studied in children [2, 17, 20]. High total cholesterol, high triglycerides, low HDL cholesterol, high uric acid, high basal insulin and high insulin responses during Glucose Tolerance Tests (GTTs) are correlated with high MBG [9] and contribute to the metabolic syndrome. BG assessments protect the OW subjects against hypoglycemia and against fear of becoming hypoglycemic.

4. Training protocol to remove conditioned meals and implement IHMP [9]

1: Suspend meals for up to 48 hours

2: Locate physical sensation of hunger

3: Measure blood glucose concentration

4: Mentally associate the physical sensation with the blood glucose 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 sensations and the measured blood glucose with the previous sensations and measurement.

5. Initial hunger (IH)

Hunger arousal was associated with low BG, to arousal of gastric activity and to a decrease in bacterial counts in the duodenum [2], thus might be the best moment for intake of energy. Initial Hunger (IH) appeared after meal withdrawal as a biophysical, subjective sensation that coincided with a recognizable (constant) physiological state of diminishing energy availability. This physiological state recurred more than once per day and suggested spontaneously energy intake in the absence of visual, olfactory or word food cues [2, 6-7, 10-11, 17]. Blood glucose marked the metabolic condition 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 individualized fasting blood glucose was used to indicate that a meal could begin [21]. In home diaries, lean adults and mothers for toddlers reported IH associated to a blood glucose that was low in 90% of occasions. This percentage decreased to 60% of meals in overweight adults and to 50% in OW children. We encountered two obese diabetic subjects who never developed hunger after meal suspension. After the age of 60, hunger sensations became week and confused.

6. Training

After the first short period of diarrhea treatment, the infants and adults were trained for 7 weeks under the researchers' revision. The first step was suspending meals until the child gave signs of hunger [6, 17]. The claim for food might consist in a change of mood from tedious to crying. Mothers assessed the children's IH before showing food or a laid table. On the first demand, before serving the meal, mothers were asked both to memorize the manifestations of restlessness and to measure blood glucose. On other occasions the same child moved around in search of food or showed what he/she wanted. The first meal was postponed from 0 to 48 h, 2 h on average after the usual schedule. At the following meals mothers repeated the learned strategies. In the interval, mothers solicited energy expenditure rather than offering new energy. Energy-dense food with more than 60kcal/100 g. was allowed initially in a limited amount but in a growing quantity after the demand for food and after eating fruit or vegetables. The portion recommended was 150g of vegetables before lunch and dinner and 200g of fruit before breakfast. The energy-dense food was calculated in such a way as to evoke a new demand soon before the time fixed for the following meal. Non-starchy vegetables (NSV) were recommended in large amounts (in adults, 300 grams per meal or half/one kg per day). This amount prevented fainting in overweight subjects [22] and allowed a smooth interruption of any consumption. Subjects decided this intake cessation when they thought that the energy already consumed allowed to reach the planned IH arousal/meal consumption. After 3-14 days training mothers had learned how to evaluate both the energy left in blood (BG) from the preceding meal and the food energy needed to cover the gap up to the time fixed for the following meal. Each time the amount of food, the content and the time of meal were allowed to be adjusted. Mothers administered more food energy in correlation to activity endurance and found a way to make their children manifest IH (demand for food) 3 - 4 times a day [6, 17-18]. NSV attenuated the drama at the cessation of food administration when mothers retained that child's energy intake was sufficient to cover the interval of time before the following planned meal. After some days of trials and errors, and occasionally, of irregular mealtimes, mothers succeeded in obtaining the child's demand/meal 3 or 4 times per day with an average error of less than 30 minutes in 90% of cases. Such alimentary rhythm is called as Recognizing Hunger or Initial Hunger Meal Pattern IHMP [6, 17]. No food category was prohibited, except for saturated and trans fats. NSV intake was positively correlated with the intensity of hunger arousal in the same meal and intended to negatively correlate with hunger intensity in the subsequent meal.

7. The feeding relation

In the Pediatric Gastroenterology Unit, mothers of diarrheic and malnourished infants were solicited by the hope for improved health in adulthood and fully engaged to avoid meals with positive energy balance [17]. The exclusion of any time interval with either positive or negative energy imbalance requires a continuous presence of the child in the mother's mind. It requires skill and attention and being prepared to an unremitting fight against conditioned intake. Mothers were the only help in recovering children, although some nurses understood and collaborated. Only one father was of help among thousands and thousands of families. The burden of achieving the health, efficiency and fortune of the future adult pertained to the mothers. Husbands helped in the creation of a calm, serene environment for this design but they did not substitute mothers in health defense and prevention, except for brief periods. At least, husbands were unable to have a continuous presence of the infant in their mind. In the current age of richness, how can mothers devolve such basilar, extremely rewarding, sometimes painful rearing to other people? Are they really able to dismiss the ideal woman that was depicted by Raffaello that survived for 500 years in Europe: a woman peaceful in her child care, with an attention focused only on her domestic environment? The model that was proposed by Giotto may be more up to date. A woman capable of taking up alone the direction of her husband's activity as well as being aware and responsible for all events in her family and outside, although in continuous contact with the child: mothers helped me by reporting everything about their infants, even when they were in their working place. One phone call allowed them to prevent contact loss from their child. As far I have worked with them, women have to maintain a dominant, direct role in rearing infants. Mothers cannot renounce to their most important and grateful enterprise, raising a human being. In this aim, we published "A plea to mothers" to suggest an intensification and an enrichment of awareness of their feeding relation with the child [23]. The "feeding relation" is a proposal in feeding children: knowing in any moment their child's current energy availability and current metabolic rate (Table 1), covering the presumed expenditure with energy rich food, perceiving any unexpected expenditure drop, any meal energy imbalance, reacting promptly to any unexplained change in the humor and in the playing through a continuous, though often marginal, albeit sufficient, attention to the child. Women in career may require additional help. Re-education of adults had obvious differences from children that here are not mentioned.

Table 1. Estimation of blood glucose by mothers on food demand from their infants in hospital just before blood sampling and autoanalyzer measurement: 54 infants demanded food before sampling, 16 infants did not demand food.

54 Demanding food		16 with no demand	
Estimation[1]	**Measurement**	**Estimation**	**Measurement**
77.4 ± 3.6[2]	74.6 ± 7.7	88.7 ± 5.9	96.3 ± 10.5[3]

Note: [1]Mothers stated whether the infant had either demanded food or not, and estimated BG just before blood sampling; [2]mean± standard deviation, mg/dL. [3]P<0.01 versus infants demanding food. (Courtesy of Ciampolini, et al., 2013 [8]; Copyright permission granted by Dovepress).

8. Deceiving blood glucose measurements

Subjects avoided blood glucose measurements taken less than 1h after consuming even few grams of food, after changes in ambient temperature, after physical activity such as walking or cycling, or under psychic stress or during fever because blood glucose in these circumstances is higher than 1h after cessation of the transient metabolic condition [9].

9. The diary

Seven-day home diaries reported blood glucose measurements before the three main meals and reported energy and vegetable intake, hours in bed and hours spent during physical and outdoor activities (weekly mean and standard deviation) and presence or absence of preprandial sensation of epigastric hunger. Infants' mothers compiled the diaries before training, after seven weeks and at the end of the 5-months investigation. Twenty-four similar diarrheic infant- mother pairs of the same age were trained to IHMP and the resting metabolic rate (RMR) was measured by indirect calorimetry in 14, and total energy expenditure (TEE) by doubly labelled water in 10 infants [18]. RMR decreased by 15.4%; TEE decreased by 15.5%, from 80.1 ± 6.9 to 67.8 ± 10.0 kcal/kg/d. In the synchronous ten day food diaries, energy intake decreased by 17.9%, from 85.7 ± 15.3 to 70.3 ± 15.8 kcal/kg/d (pre/post $P < 0.001$) after intervention. No difference was found between TEE and energy intake at recruitment, at final assessments and in the pre/post decreases. The height Z-score increased significantly, while weight growth was normal. Thus, the null hypothesis between conditioned and demanded (IHMP) meals is rejected.

We did not trust such re-education in adults, even though Ayurveda teachers reported good results. We always required an objective assessment and after the first training days, we asked adults to write the presumed blood glucose before measurement. Adults in training were often surprised to being able to predict the measured blood glucose (Figures 5 and 6).

Fourteen out of 46 trained subjects who were not hungry had BGs below 87 mg/dL, the maximum limit of blood glucose of those who were hungry (Figure 6). These 14 subjects showed an average estimation error of 4.5 ± 3.1% of the measured blood glucose, which did not significantly differ from the estimation error of the 18 trained subjects who were hungry [9]. Thus we included weakness (inanition) into IH.

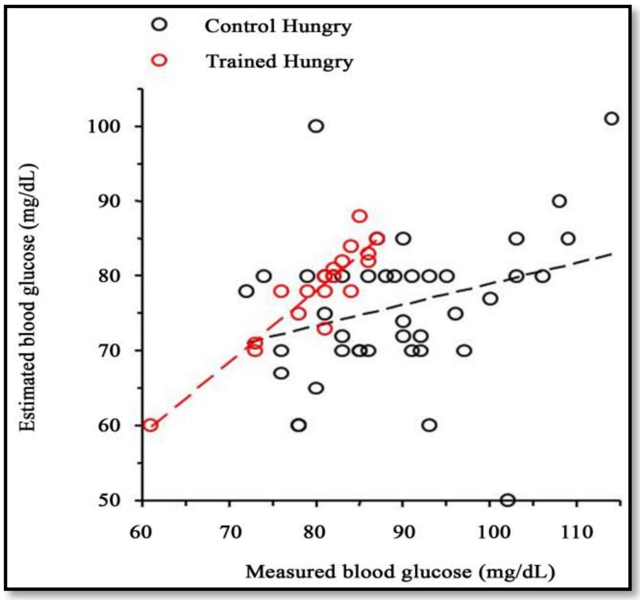

Figure 5. Estimated vs measured blood glucose of subjects reporting to be hungry at the final laboratory investigative session.

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). (Courtesy of Ciampolini, Bianchi, 2006; licensee BioMed Central Ltd under the terms of the Creative Commons Attribution License <http://creativecommons.org/licenses/by/2.0>

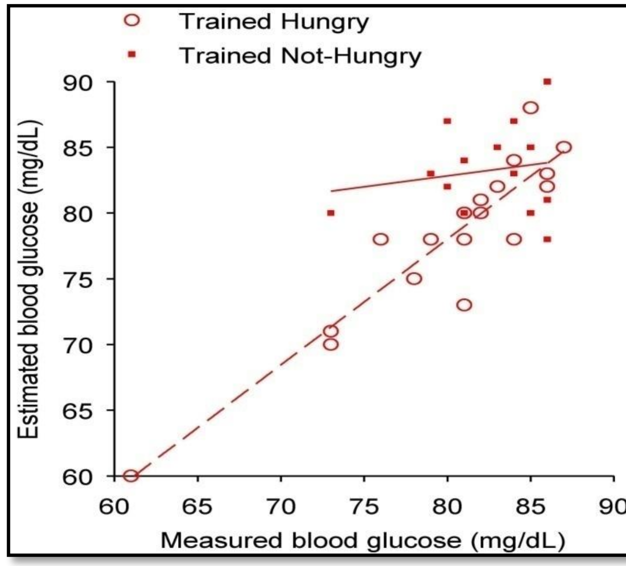

Figure 6. Estimated vs measured blood glucose of trained subjects with levels below 87 mg/dL at the final session. The highest glycemic value measured in trained hungry subjects was 87 mg/dL. Below this value of measured blood glucose, 18 subjects reported to be hungry (hollow red circles) and 14 subjects were not hungry (full 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 Ciampolini, Bianchi, 2006; licensee Bio Med Central Ltd under the terms of the Creative Commons Attribution License http://creativecommons.org/licenses/by/2.0.

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

Humans recognize sounds and colors. Do adults learn to recognize children' hunger manifestations (and gastric sensations of hunger in themselves) that arise after meal suspension from conditioned hunger sensations? How wide may be the difference between the blood glucose subjective estimation and the biochemical measurement? [9]. In these circumstances, we measured blood glucose by autoanalyzer that has 1% error in repeated measurements. In our studies, adolescents have the lowest BG estimation error and people over sixty the highest. We studied estimation error in diarrheic infants and in adults who were less than 60 years old (Figure 5). The distinction involves all energy metabolisms. Twenty-four diarrheic infants in the 2nd year of age were trained to IHMP and the resting metabolic rate (RMR) was measured by indirect calorimetry in 14, and total energy expenditure (TEE) by doubly labeled water in 10 infants. RMR decreased by 15.4%; TEE decreased by 15.5%, from 80.1±6.9 to 67.8±10.0 kcal/kg/d. In the synchronous ten day food diaries, energy intake decreased by 17.9%, from 85.7±15.3 to 70.3±15.8 kcal/kg/dafter interventions (pre/post P<0.001). No difference was found between TEE and energy intake at recruitment, at final assessments and in the pre/post decreases. The height Z-score increased significantly, while weight growth was normal. Thus, differences in blood glucose, in blood glucose recognition, in energy intake, in RMR and TEE reject the null hypothesis between conditioned and demanded (IHMP) meals. The training consisted of blood glucose measurements at hunger arousal for two weeks to validate the subjective hunger sensations. One month later 64 trained and 72 control subjects came to the hospital lab before breakfast following an overnight fasting [7, 9-10]. All subjects declared current presence or absence of hunger and estimated blood glucose. A glucose autoanalyzer measured the actual blood glucose (Figure 5 for adults, Table 1 for infants). The number of control adults (42 out of 72) stating hunger was significantly higher than the number of hungry trained subjects (18 out of 64) [9]. All hungry adults described hunger sensations as gastric emptiness or gastric pangs. In the hungry trained group, the mean estimated blood glucose was 78.1±6.7 mg/dLand the mean measured value was 80.1±6.3 mg/dL. This measured blood glucose 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 blood glucose 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) adults do not reflect their biochemical condition when stating hunger and when estimating blood glucose. In the hospital lab, control adults asserted their blood glucose and hunger state some minutes before having breakfast. Right after responding about hunger, control adults 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 habit to compare current sensations to past experiences. Humans tend to maintain constant blood glucose before meals (confidence interval ± 3.8 mg/dL around MBG in a week). Control adults who asserted to be hungry, did not state levels that were lower than their personal, habitual high BG [9-10]. Only 8 out of 42 controls stating to be hungry had low blood glucose estimation error [9: Figure 5). Except for this minority, control adults described (reported) conditioned hunger. Even if they sensed peristaltic hunger gastric movements, these endured poorly. All these differences are modest, the main difference consists in the onset of hunger sensations: either before focusing on food (after meal suspension) or after focusing on food (conditioned). Low blood glucose can confirm this distinction. When doubts persisted, meals could occasionally consist of NSV only.

11. Not-hungry adults (hunger equivalents)

At the final investigative session, the trained and control adults that were not hungry significantly underestimated their glucose levels. Their estimation errors were respectively: 4.8± 3.2 mg/dL and 16.1 ± 11.3 mg/dL in trained and control groups. The linear correlation between estimated and measured blood glucose was highly significant in the trained group and not significant in controls. The difference between trained and control groups did not depend on gender, age, number of years at school, weight, or body mass index. Under 87 mg/dL, estimation error was low in both trained and control groups apart the adult's statement on hunger (Figure 5). In adults with values above 87 mg/dL of BG, the estimation error increased significantly. Despite their not being hungry, 12 out of 14 trained adults under 87 mg/dL and 3 out of 32 above 87 mg/dL described the slight sensations they employed to estimate blood glucose concentrations. Thus, compared to controls, who did not report equivalents of hunger (n = 30), a significantly higher proportion out of the 46 not-hungry trained adults was able to report sensations different from gastric hunger, which were useful in estimating their blood glucoses, and this ability prevailed below 87 mg/dL. In their reports, these 15 adults described physical (3) or mental (10) weakness or abdominal changes in tension or movement (2). Six out of 46 not hungry trained adults, but none of the control adults, had felt gastric IH before entering the hospital for the final session; however the sensation faded while waiting for blood sampling. In the not-hungry adults' reports, the sensations of mental weakness consisted of difficulty in sustained mental concentration, impatience, irritability, drowsiness, gnawing sensation, loss of enthusiasm and effectiveness at mental work, or poor mood at their jobs. The 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 signaled a change from a former sedentary life-style. This sensation was used regularly to indicate a signal of meal need with an increased requirement of high-energy-dense food for the following meal(s). The prevalence of these 'hunger equivalents' ranged from an occasional occurrence to less than 15% of meals in phone reports. Two adults reported that they never sensed (gastric) hunger, but estimated blood glucose within 6% estimation error always by assessing mental or muscular weakness during training or during the final investigative session. In their reports, these adults consumed meals at blood glucose estimation between 78 and 85 mg/dL. Also Caudwell found weakness and low RMR as signals for starting meals [24]. We recently, encountered two obese adults who denied any hunger arousal after 48h fasting. The two adults were diabetic type 2. They decreased their body weight by more than 15% and before dinner BG decreased to 75.3 mg/dL. This value is inside Low BGs in the figure 5.During hunger weakness, blood glucose, blood glucose estimation error and RMR have low values [7, 9-10, 24]. These characteristics suggest that hunger weakness is a reliable signal for intake just like hunger pangs.

One out of 89 trained adults [10] reported not having gastric sensations at all, even long after consuming a meal. We exceptionally suggested meal start after estimation of blood glucose decrease to lower than 81.8 mg/dL. The adult endured physical weakness for two hours before meal consumption, blood glucose lowered from 92.5±5.1mg/dL to 80.7±5.7 mg/dL and body weight from 74.5 to 67.4 kg after 36 days. The adult coped with an open air heavy job during cold winter. At recruitment, he was 189.5 cm tall with a BMI = 20.75. His energy intake showed a decrease from 3613±615 kcal/d to 1817±394 kcal. We suggested to this adult to use the sensation of physical weakness as IH and as an appropriate signal for meal onset. In the following 40 days, the adult increased intake to 2380±459 kcal, blood glucose to 85.6±4.7 and weight to 70.95 kg. In the meantime he had solved recruitment complaints (abdominal pain and dermatitis). This 'case' is something more than anecdotal. It is unrepeatable and suggests the need for higher blood glucose than 76.6±3.7 mg/dL for subjects engaged in intense, daylong physical exercise [10]. 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.

12. Adapting energy intake to energy expenditure

In table 2, we report final values in 27 adults who remained at high MBG out of 89 who practiced IHMP for 5 months [10]. Six out of 27 were engaged in heavy manual work in a cold, open air climate. They asserted to comply accurately with IHMP and their high insulin sensitivity at GTT supported their assertions. Heavy physical activity in a cold climate may require high blood glucose and impose IH arousal when blood glucose is high for sedentary people. In our investigations (Figure 3 & 4), intestinal functions and xylose absorption increased their rate during cold exposition in association with an increase in resting metabolic rate [15-16]. Adjusting energy intake according to hunger delay or anticipation is useful to maintain steady, optimal blood glucose (energy availability). IHMP consisted in a meal by meal exhaustion of nutrients added to blood with the last meals to prevent absorption slowdowns and to avoid slow intestinal absorption, bacterial growth, immune stimulation increase and diarrhea relapses. In the first decade of our studies in a pediatric ward, we did not measure blood glucose before meals and we limited children's intake by administering food only on demand [11]. The limit in intake was not biochemical [6-7, 9-10, 18]. In the occurrence of a discrepancy (hunger arousal and high blood glucose), we suggested mothers (and adults for themselves) to let prevail the hunger manifestations (IH arousal and IHMP). The infant did not suffer hunger endurance, its intake had a limit and most times the limit was easily recognizable.

Table 2. Heavy outdoor manual work (6 High BG) vs. a sedentary lifestyle in 21 High BG of 27 (out of 89) adults who failed to reach Low BG (76.6 ± 3.7 mg/dL) at study end.

Parameters	6 High BG	21 High BGab
Final Mean blood glucose (mg/dL)	86.4 ±4.0	87.1 ±5.3
Final insulin AUC (mU/ L/3h)	124 ±26	207 ±99 c
Final blood glucose AUC (mg/dL/3h)	536 ±56	601± 82 d
Final Insulin sensitivity index	11.4 ±2.9	6.68 ± 4.0 e
Final Beta cell function index	1.29±0.66	1.43± 1.22

Note: a Six High BG subjects reported doing heavy work all day in outdoor environment during cold weather and reported accurate compliance with IHMP. No significant differences in the five parameters from recruitment. At recruitment, MBG was 86.9 ± 5.3 mg/dL in 27 High BG subjects; b The 21 High BG subjects included 15 that were Low BG after 7 weeks training (diary assessment) and six who had higher MBG than 100 mg/dL at recruitment;

c $P < 0.01$; d $P < 0.05$; e $P < 0.001$. AUC: area under curve during glucose tolerance test. (Courtesy of Ciampolini, Sifone, 2011 [10]; Copyright permission granted by Dove press).

13. IHMP and malnutrition

MBG is positively associated with insulin resistance in depressing intestinal functions, perturbing the microbiome and developing an overall subclinical state of inflammation. In turn, this state produces functional diseases like asthma, arthritis, bowel disorders and a long term evolution to metabolic, vascular and malignant risks. Meals with excessive energy intake are signaled by high BG before the following meal and this suggests corrections. The consequent energy availability becomes lower during IHMP than during a conditioned meal pattern. A meal pattern dictated by IH arousals lowers energy intake, BG and insulin resistance; this meal pattern maintains body weight in lean subjects, prevents risks and is freely chosen by a third of population before any training. A controlled study was carried out in 9 undernourished infants. Demanded meals were associated with low preprandial BG, significantly lower energy intake, prompt recovery from diarrhea and slow recovery of lean body mass in two years. Another study documented the recovery of 12 years old boy from severe malnutrition by implementing IHMP. The boy decreased MBG from 98.9±15.1 mg/dL to 78.6±2.9 mg/dL. This boy grew from a Gomez index of 56% (10.7 BMI) at recruitment to an index of 80% (19.6 BMI) at the age of 20. Undernourished people are often in an intestinal disordered condition for insulin resistance that impairs the passage of nutrients absorbed from blood into lean body tissues. These facts and observations suggest together that IHMP is necessary to prevent alterations of the microbiome and to avoid an immune, reversible deficiency from birth onwards.

14. Summery

- In infancy or adulthood, humans can learn to recognize Initial Hunger arousal at the same blood glucose, 76.6±3.7 mg/dL in a sedentary activity. This means that IH corresponds to a reproducible metabolic condition that can be identified and recognized by humans.
- Initial Hunger arises after a meal suspension of 0 - 48 hours in healthy children and healthy adults but not in obese diabetics.
- An Initial Hunger Meal Pattern (IHMP) consists of the IH arousal three times a day. Practicing IHMP is associated with insulin sensitivity, low energy intake (-17.9%), low MBG (-15 to -20%), low RMR (-15.4%) and low TEE (-15.5%).
- The individual regression toward an even energy balance under IHMP was proportionated to the value at recruitment.
- About a third of healthy people shows at recruitment (before any training) the same Low MBG, low RMR and the associated insulin sensitivity that are gained by people after training IHMP.

15. Conclusion

Among Scientists, there may grow a consensus on few basic principles to avoid the risk of accepting all results as well as the contrary demonstrations. The finding that the same intervention, Initial Hunger before meals, protects both undernourished and overweight subjects is based on a basic finding that seems difficult to suppress: more than half immune cells of the body reside in small intestinal mucosa. This means that any Medical intervention on diseases that involve immunity have to care of not increasing immune stimulation. I wonder if there are diseases that do not involve immunity, earlier or later!.

16. Conflict of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

17. Acknowledgment

NA

18. List of all abbreviations

BG = Blood Glucose, an index of energy availability in blood for the whole body.

GTT = oral glucose tolerance test.

AUC = area under curve of GTT.

RMR = resting metabolic rate.

TEE = daily total energy expenditure.

OW = overweight, BMI > 25; NW = Normal body weight, BMI under 25.

BMI = body mass index = body weight in kg divided by squared height in meters.

19. List of Terms

Initial Hunger Meal Pattern (IHMP): Energy intake is adjusted to three arousals of initial hunger per day.

IH = Initial Hunger = Sensations of hunger associated with low blood glucose.

MBG= mean blood glucose: mean of BG measurements in a week.

NSV = Non-starchy Vegetables

Initial Hunger: This consists of gastric pangs or physical weakness.

High Blood Glucose: This is blood glucose of over 82 mg/dL.

Low Blood Glucose: It is blood glucose below 82 mg/dL.

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