
New findings on energy balance and established wisdom

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Abstract: Background. Energy balance in blood and body may differ for a day or two although compensating in a month. Most people (60%) maintain a positive energy balance and a high blood glucose (BG) high energy availability in blood and high resting metabolic rate that correspond to insulin resistance/fattening and ill health. A meal/satiety pattern dictated by the rhythmic arousal of Initial Hunger (IH and IHMP) improved exhaustion of the energy consumed in previous meals and decreased high energy intake, high preprandial BG, high resting metabolic rate (RMR), insulin resistance, overall subclinical inflammation, vascular risks, deteriorations and functional disorders. Methods. We defined Initial Hunger as sensations that spontaneously arise after eating suspension. IH consistently arouse in different groups when BG declined toward 76.6 ± 3.7 mg/dL. A week diary reported assessments of IH and preprandial BG measurements before the three main meals. Mean BG in a week was stratified within normal BG limits, but different subjects pertained to different strata. Thirty-one untrained control adults maintained his/her own mean and BG stratum for five months. After training, these subjects changed his/her own mean BG to the stratum that was associated with IHMP. Measurements reported by diary, of RMR and of total energy expenditure demonstrated this stratum change. From recruitment, the mean decrease was 15.4% by indirect calorimetry and 15.5% by doubly labeled water in a total of 24 toddlers ($P < 0.001$). Mean BG thus assessed the deviation of a meal pattern from the mean BG associated with IH (IHMP). Results. In San Diego ASN 2014, we showed the effectiveness of IHMP on regression of fattening/insulin resistance for a long term in 181 adults of mixed body weight who had bowel functional disorders and were clinically normal. However we had earlier designed IHMP for a broader aim as compared to a body loss device. We wanted to educate children and future adults to an intestinal low immune involvement and to the best fitting of intake to body regulations. Thus, we tried to publish the recovery of diarrhetic malnourished infants by IHMP in an American Society for Nutrition (ASN) Journal. Subjects were aged less than 15 months, had lower body weight per age than 70% and recovered through many months and years. This aim was right opposite to weight loss. The ASN Journal rejected the publication as findings of clinical but no nutritional interest. Med Crave promptly published the findings. In a broader thought, the ASN Journal protected the established assistance beliefs and trusts from the confounding intrusion of an innovative, self-help system (IHMP).

Keywords: Energy Balance, Meal Energy Load, Malnutrition, Overweight, Immune Improvement

1. New Findings

In the nineties, we published a decrease in energy intake in association with elimination of diarrhea relapses in toddlers after meal administration at demand for food [1,2]. Subsequent papers confirmed these results and emphasized the long persistence of the taught meal pattern [3, 4]. This time-consuming training had the purpose of contrasting fattening/insulin resistance in the educational formation of the future adult. In Western countries, some 60% of the population fail to adequately limit food intake and two thirds become overweight or obese; 5% - 10% develop

diabetes [5 - 9]. Few dieticians would disagree that hunger is a signal for starting a meal, but simply suggesting to patients that they should eat when hungry is not likely to bring about improvements in food intake regulation. This is because assertion to be hungry is subjective, and corresponds to different energy availability in blood from an individual to another [6]. We were used to observe children in an hospital ward at their meals. Some children cried before food administration, but those who did not cry ate the administered meal as well as those who cried. By receiving no food, the not crying infants went on quietly for hours. Our findings suggested no exhaustion of energy of

previous meal at each of these customary (conditioned) meals [10 - 12]. Common wisdom suggested that a lower meal intake might automatically and unconsciously compensate the incomplete pre-meal exhaustion. On the other hand, omission of a meal might weaken the infant as well as adults. This objection consists in the mistake that hunger is only an epigastric sensation. Yet Initial Hunger may present as weakness, that is substantiated by a decrease in blood glucose (BG) and in resting metabolic rate. This weakness corresponds to the exhaustion of energy of previous meal, represents a form of Initial Hunger and is a good signal for meal consumption (See next chapter).

We based our medical intervention on physiological relations in the alimentary canal and direct observation of infants. The intention was to better fit meals to the physiological reflexes of intestine and to the phylogeny. Blood glucose (BG) represents a dynamic balance between influx and efflux of energy in blood, and indicates energy availability to body [13 - 15]. The cumulated energy balances determinate BG lowering down to the lowest levels in a day (=before meals). The exhaustion level is objectively comparable among individuals because it arises at an identical, definite moment of energy availability, the lowest in the day. We had the chance to study a group of 89 adults that lost weight when insulin-resistant or overweight and maintained weight when lean and insulin-sensitive [6, 16]. This “homeostatic” group exhausted energy meal by meal, habitually. In this group, we searched the point of complete exhaustion 3 hours after intake of 300 kcal. In Figure 1, the lower red line pertains to the mentioned mixed BMI group of 89 subjects. The final value of this group shows exhaustion of previous intake at about 75 mg/dL [16]. This value is significantly lower than the final BG of groups eating at libitum. The meal pattern associated with regular preprandial exhaustion implies lower energy

intake and we found this in all our randomized, controlled studies.

2. Initial Hunger (IH)

We ordered to suspend any meal and any thinking to meals, to go on with own job or playing, watching to the arousal of a sensation of hunger for 48 hours, measuring BG at the arousal and taking note of the characteristics of the hunger sensation as well as of BG value [17]. At subsequent arousals of hunger, the subject could recognize identity of sensation and BG. Many people had a lag time of hours of happy activity although no intake before the first hunger arousal. The distinction between IH and habitual (conditioned) hunger was demonstrated by the simultaneous BG measurement. Two months after training for two weeks, 64 trained and 72 control subjects attended the hospital lab before breakfast after an overnight fasting. All declared current presence or absence of hunger, and estimated BG. A glucose autoanalyzer measured actual BG. Results of this study are reported in Figure 2 [17]. We obtained similar results in a study in children after training in IHMP [18]. A minority of control subjects (Figure 2) had low BG and showed a low error of estimation. We found such minority in all groups at recruitment. The low estimation error demonstrates that these minorities may identify a sensation similar to IH as reference for eating in absence of any training. Given this natural relation to intake in minorities of all studies, and the attainment of similar BG in GGTs of the homeostatic group, as well as the association with insulin sensitivity, IH may represent a physiological signal (natural instinct) that was developed in the phylogeny to guide energy balance to best survival. Initial Hunger (IH) corresponded just to this value in 4 separate studies on mean week BG obtained by home-diaries with 21 preprandial BG measurements [6, 17 - 19].

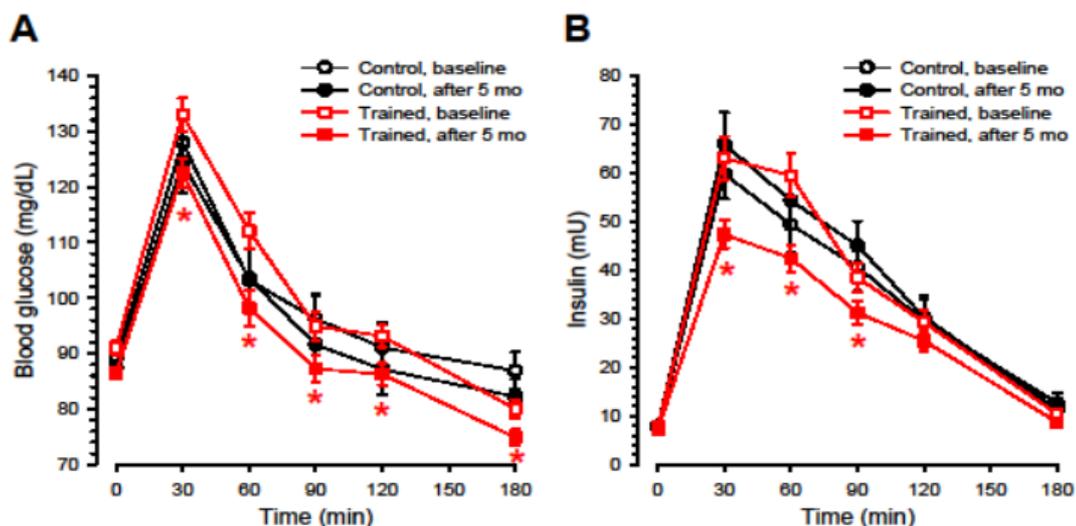


Figure 1. The lower red line pertains to a mixed BMI group of 89 subjects. Overweight and Normal-weight (NW) insulin-resistant subjects lose weight. NW insulin-sensitive subjects maintain stable weight. I.e. The final value indicates exhaustion of previous intake and is about 75 mg/dL. Image courtesy of Ciampolini M, et al. [16].

Only ignoring all these demonstrations, experts from NIH (US) dared to assert that *there is nothing particularly innovative about this IH proposal. Attention to internal cues to address eating patterns has been a part of standard cognitive behavioral weight loss treatment for quite a long time.* To allow intake, common wisdom rely on a state associated with the determination of eating (will to eat). The state may give rise to sensations and physiological reflexes. This arousal is conditioned by cues associated with eating and happens within the habitual stratum for intake (next paragraph). Our innovative work consisted in suggesting eating suspension and Avoidance of conditioning cues to escape from the habitual stratum as an initial, reference step in training.

2.1. Recognizing Hunger Before Each Meal: Metabolic Consequences

A total of 181 subjects aged 18–60 years were recruited between the years 1995 and 2000. All subjects entered a randomized controlled study in which the primary outcome was weight [5]. One-hundred and forty-nine subjects completed the full study on body weight and 120 subjects completed a second study whose primary outcome was insulin sensitivity [5, 6]. Sixty-six NW subjects and 38 OW subjects were trained in Hunger Recognition over a 7-week period then followed for a further 3 months.

2.2. Body Weight

Hunger Recognition was associated with significant decreases in body weight and body mass index (BMI) in OW subjects compared to controls after 7 weeks of training and after 3 further months of application [5]. BMI decreased from 28.7 ± 3.5 to 26.5 ± 3.5 in the trained group. The decrease was significant in comparison to controls ($P = 0.004$) and in comparison with baseline values of the same group ($P = 0.0001$). Multivariate analysis of variance showed a significant association between training and both BMI and weight. Pre-meal BG emerged as the most significant predictor of variations in BMI and body weight [5]. NW subjects maintained weight overall; however, those trained NW subjects whose BG was high at recruitment also lost weight compared to controls [6].

3. Stratification of Energy Availability, Insulin Sensitivity (and Metabolic Health)

A week diary reported food intake, the assessment of IH and the preprandial BG measurements. Mean BG in a week was stratified within normal BG limits but different subjects pertained to different strata. Each person maintained the own level after five months. Mean BG allowed thus to ascertain the deviation of each meal pattern from the mean BG associated with IH (IHMP). The

stratification by mean preprandial BG is positively associated with insulin resistance and vascular risks and is similar (in correlation) to the stratification between glycated hemoglobin and vascular hazard ratios [6, 20]

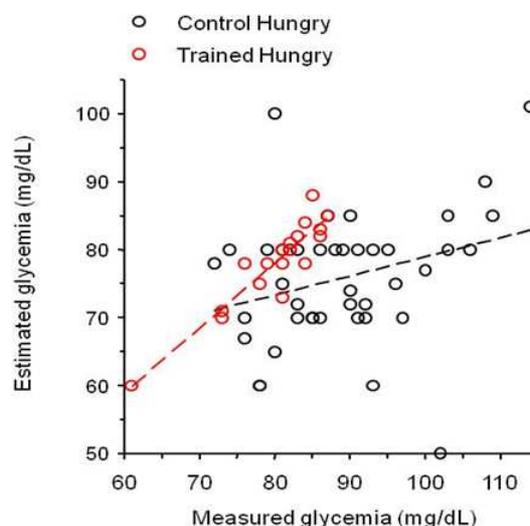


Figure 2. Two months after training for two weeks, 64 trained and 72 control subjects attended the hospital lab before breakfast after an overnight fasting. All declared current presence or absence of hunger, and estimated BG. Actual BG was measured by a glucose autoanalyzer. Image courtesy of Ciampolini M, Bianchi R [17].

The second study included 120 adults, mean age 33 years, of mixed body mass index (BMI) addressed to the Gastroenterology Unit for functional bowel disorders. At recruitment, the 120 subjects showed mean BG at one personal level of ten possibilities [6]. Thirty-four subjects were below 81.8 mg/dL (LBG) and 55 were over (HBG). Thirty-one control subjects did not change their mean BG after 5 months. The 34 LBG trained subjects only decreased weekly-diary BG standard deviation in comparison with controls. The 55 HBG subjects showed higher mean insulin resistance, HbA1c, other cardiovascular risk factors, and higher bodyweight compared with the 34 LBG subjects. A total of 41 out of the 55 HBG subjects regressed to LBG with training. After training, only HBG subjects, compared with HBG controls, significantly decreased preprandial BG from 91.6 ± 7.7 mg/dL to 81.0 ± 7.7 mg/dL, in association with a decrease of HbA1c from $4.81\% \pm 0.44\%$ to $4.56\% \pm 0.47\%$, of GTT insulin AUC from 244 ± 138 mU/L to 164 ± 92 mU/L, and of energy intake from 1872 ± 655 kcal to 1251 ± 470 kcal ($P < 0.001$), with an increase of indices of insulin sensitivity from 5.9 ± 3.3 to 9.8 ± 5.6 and of beta cell function from 1.0 ± 0.7 to 1.4 ± 1.1 ($P < 0.05$). The wellbeing, nutrition, and cardiovascular trials showed no significant differences between trained and control subjects in the LBG group. In the trained HBG group, the decreases in days with abdominal pain or stomach ache, in diastolic blood pressure and in LDL to HDL cholesterol ratio, and

the increase in the HDL cholesterol were significant and significantly larger than in the control HBG group ($P < 0.005$) [6].

4. Findings in Undernourished Infants

The healthy small intestinal mucosa contains half immune cells in human body [21 - 43]. The immune cell number is heavily influenced by bacteria in experimental studies in germ-free animals, and immune activation promotes diarrhea [21 - 43]. We counted bacteria on intestinal mucosa of 126 children, and found a significant decrease with passage of time since the previous meal. The difference was 39 times on atrophic, celiac mucosa and 11 times on normal mucosa [39]. Five % to fifteen % of intestinal bacteria are immunogenic [34]. During digestion, a low bacterial growth might be a sound, hygienic principle. We postponed food administration until arousal of the first hunger manifestation but no longer than this, and thus prevented relapses [1 - 5]. After adoption of IHMP, energy intake decreased about 20%, total daily expenditure by 15.5%, resting metabolic rate by 15.4% [19]. IHMP could reduce high energy intake, incomplete exhaustion of the energy consumed in previous meals, high preprandial BG, high RMR, insulin resistance, and a list of associations: immune involvement in intestinal mucosa, overall subclinical inflammation, vascular risks, deteriorations and functional disorders.

During the forty years of activity of the pediatric Gastroenterology Unit of Florence University, we randomly assigned each subject to control and intervention groups. The largest groups consisted in diarrheic children. The aim of this large, prospective study was a prevention from fattening/insulin resistance and diabetes. We investigated also 6 trained mother/child pairs in comparison with 3 control pairs (Figures 3 and 4) [44]. We conceived IHMP to improve intestinal absorption by decrease of immune involvement in intestinal mucosa as well as throughout the body (overall subclinical inflammation). The nine malnourished infants had a weight per age lower than 70% and chronic diarrhea in the first 15 months of age. 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 under intervention for 5 total times in two 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 4 or 5 events every 60 days persisted in control subjects 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. 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 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 in treated infants increased per age from recruitment 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. These differences were not significant at single times but were significant by chi square for trend ($P < 0.01$). Psycho-motor development was normal except for one control infant.

We conclude that high triglycerides and insulin resistance are involved in the development of persistent diarrhea, overall subclinical inflammation and malnutrition in these undernourished infants as in the development of functional bowel disorders and overweight in adults [6]. IHMP was effective for the long maintenance in malnourished infants [44], in diarrheic infants [3, 4], and in overweight people [5]. We studied 43 trained and 43 control children from the second to the eleventh year of age. The children were diarrheic in the second year but soon recovered from diarrhea. At the mean age of 10.1 years, the increase in % weight for height was $3.1\% \pm 12.5\%$ and $10.3\% \pm 13.7\%$ in trained and control subjects. The longitudinal difference was significant at $P < 0.05$.

Considering together effects of IHMP on malnourished infants, on chronic diarrhea, on vascular risks and fattening/diabetes, considering the spontaneous maintenance by a minority of population and considering the long term maintenance of the skill and intention to limit intake, considering the association of IHMP with low intake and low total energy expenditure as well as low RMR, high insulin sensitivity, low vascular risks, we conclude that IHMP is a safer way of eating than ad libitum intake.

5. Common Wisdom

At the 2014 ASN (EB) San Diego meeting we presented: "Learning sensations of pre-meal hunger: effects on energy intake, body weight and insulin sensitivity". A written version (MS ID#: ADVANNUT/2014/006346) will be available. The use of IHMP seemed as a device for weight loss but this was misleading. Thus I submitted to the Journal of Nutrition (ASN) the above research investigation: "Initial Hunger" for all? A study on undernourished infants" [44]. The intention of the submission to J Nutrition was to correct the view on IHMP as an only body weight loss device. ASN (J Nutrition) refused this meaning, and considered the manuscript as a clinical study on malnutrition to be addressed to a clinical Journal. This limitation is in contrast with the intention of the expert (researcher, i.e. myself) to widen the application of IHMP. This type of divergence (between the established authority

and the expert) has been well debated since Plato and Aristotle. Feyerabend recently emphasized the distress caused by Galileo's findings in the Authorities and population of his age [45]. The distress did not simply consist in a power diminution for the established Authorities. A well consolidated outlook was overturned and the population entered a uncertain state about actual events, facts and about trust attribution, a disordered state. Current societies rely and trust on the activities of a big number of experts in thousands of different matters. The single person is an expert in his/her own job but has to rely and trust on someone who is competent in other matters. Institutional authorities preserve this network of established trusts to maintain efficient activity, production and order for all. The institutional Authority may try to stop novelty intrusion. I operated in a University hospital but the director did not refrain from protecting young physicians from the observed achievements: we all think the same, only you have a different thinking. Oh well, like in Breshnev's Russia!. I repeated. The scientist/researcher faces the Promethean myth, and may be happy with the open mind of ASN, at least in comparison with old Italy and worse, with Breshnev's Russia. Novelty diffusion was worse before Internet. Referees evaluated the submitted manuscripts by consolidated wisdom. Few fields were open to innovation: genomics, virology, epidemiology, drugs. The association between insulin resistance and overall inflammation was proposed in 1923 and 1963 [46, 47], but was accepted in 1988 [27]. The explosion of internet Journals overthrew the relations with authors, and Journals seem now to beg authors to submit manuscripts. Does still exist a Scientific Journal hierarchy? Yes, it consists in the impact factor. Is it useful for knowledge diffusion? Currently exists internet, the limitation to innovation is bland, although being noxious because may sustain easy, well consolidated ill beliefs and associated patterns. Presumably, a new hierarchy will develop, and limitation will grow and impair again knowledge progression. It is human!

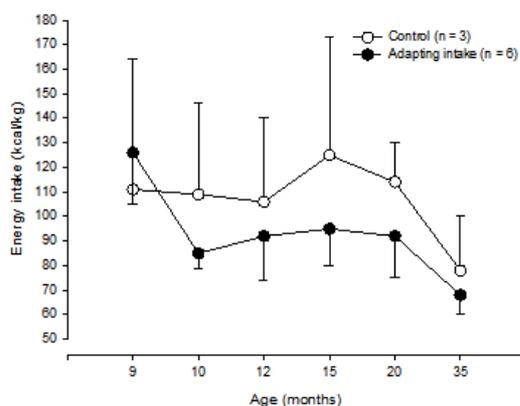


Figure 3. Daily energy intake in treated (6, black circles) and control (3, white circles) subjects during two follow up years. $P < 0.05$ in the longitudinal comparison between decreases from the assessment at recruitment and subsequent assessment. Image courtesy of Ciampolini M, et al. [44]

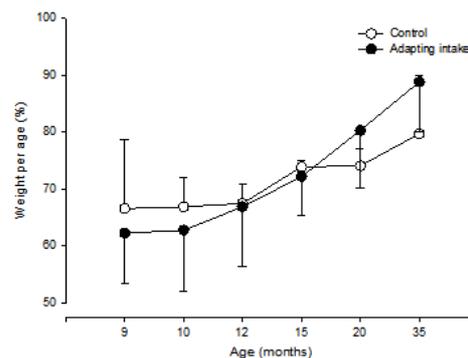


Figure 4. Symbols like in Figure 1. Image courtesy of Ciampolini M, et al. [44].

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