

Eliciting Clear-Cut Initial-Hunger at Proper Time

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Abstract

Bringing up children to scheduled meals promotes current extent of overweight and insulin resistance. The spontaneous arousal of hunger sensations at low blood glucose concentration is different from scheduled arousal. Memorization of spontaneous arousals and reports of their identity in later occasions may be confirmed by biochemical, physiological and physical measurements stating the identity of metabolic conditions. This review reports this distinction and the identification by training of initial hunger (IH). Validated IH includes epigastric sensations (the most frequent and recognizable) and mental and physical sensations. A meal pattern solicited by validated IH may be maintained for months and years up to old age. This pattern reduces energy intake by a third, and decreases mean weekly preprandial BG, glycated Hb, insulin resistance and body weight in those who are insulin resistant or overweight.

Keywords: Hunger; Intake; Meals; Energy; Homeostasis; Blood glucose; Meal pattern; Intake habit; Overweight

Abbreviations: BMI: Body Mass Index (body weight in kg/square height in m); BG: Blood Glucose Concentration (glycemia); HBG: High Mean BG (> 81.8 mg/dL); LBG: Low Mean BG (< 81.8 mg/dL); IBS: Irritable Bowel Syndrome (20 years ago) currently functional disorder of bowel; IH: Validated Initial Hunger Sensations; epigastric and of mental or physical weakness; IRMP: in infants, Initial Request Meal Pattern; IHMP = *recognizing hunger*: in adults, Initial Hunger Meal Pattern; Mean BG: mean of 21 preprandial blood glucose measurements reported by 7 day diary; BG estimation: During training: writing the expected BG value in the minute before measuring the blood sample by glucometer. After training and validation: Evaluating one's own current BG value without measurement; NIDD: Non Insulin Dependent Diabetes Mellitus; TBGD: Transient Blood Glucose Decline, at least 5% for 5 or more minutes

Introduction

The adverse effects of obesity are well known and include cardiovascular disease, type 2 diabetes and hypertension as well as gall bladder disease, osteoarthritis, endocrine disorders, sleep apnea, social exclusion, depression and increase in all causes mortality [1,2]. More than 1.1 billion adults worldwide are overweight, and 312 million of them are obese [2]. Ten per cent of school-aged children world-wide are estimated to be overweight, and of these, one quarter is obese [3]. With a prevalence of overweight children at over 35% and obese children over 13% (2003-2004 figures) the United States population is among the most obese in the world [4]. The prevalence of overweight children is lower in developing countries but is rising [5]. A prospective investigation involved three separate cohorts that included 120,877 U.S. women and men who were free of chronic diseases and not obese at baseline with follow-up periods up to 20 years. The relationships between changes in lifestyle factors and weight change were evaluated at 4-year intervals. Specific dietary and lifestyle factors resulted to be independently associated with long-term weight gain [6]. Persistent high hormonal levels an year after weight loss (ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide and also a significant increase in subjective appetite) suggest long-term strategies to counteract this change and to prevent obesity relapse [7]. Bringing up children to scheduled meals may promote current diffusion of overweight and insulin resistance. We sustained this hypothesis by published and unpublished researches and practical application through 40 years. We summarize here findings and observations to improve energy balance and health, by approaching the following aspects:

1. What is *initial hunger* (IH)?
2. Effects of a meal pattern signaled by IH.
3. Amount of energy intake per meal. What is the best inter-meal interval?
4. Factors affecting clear cut arousal of IH. Environmental temperature and humidity, physical activity, lean body mass, learning, content of previous meal, like vegetables, fruits, fats, type of fats and proteins, emptiness of small intestine at meal onset, age over 60.

Point 1: Initial hunger

In the 2nd year of life, a meal pattern that offered food to infants only after their request was sufficient for body growth and usual daily activity [8,9], although it was associated with 30% energy intake decrease. In the Western countries, children are accustomed to scheduled meals, and adults actually eat at scheduled mealtimes. Hunger has been reviewed recently [10]. The sensation is not merely mental, but coincides with a complex physiological function that may rise approaching the table or solicited from good food. After completion of absorption, the small intestine develops migrant motor complexes [11]. These are powerful constrictive and propulsive movements (waves) that descend in rhythmic sequence along the small intestine for 30-40 centimeters. A subsequent wave starts in about the middle of the previous wave after 3-30 minutes. The wave coincides with subject's reporting hunger [11-13]. In animal experiment, gastric and pancreatic secretions arise together with waves. Hypothalamic centers govern the digestive activation. Here neurons respond to hormones, afferent nerves, blood glucose (BG) and insulin concentrations. Hypothalamic centers activate the small intestine, the liver and part of the large intestine through the vagal nerve and hormones. This activation takes place at a Transient BG Decline (TBGD). These TBGDs arise together with hunger epigastric sensations, at about 80 mg/dL of BG, and may depend on insufficient glucose influx into blood [13-15]. Is exhaustion

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of liver glycogen the *primum movens* of hunger function? The final hour(s) in the interval between meals are mainly covered by influx of fatty acids from adipocytes and amino-acids from muscles [16].

This complex function is activated by insufficient energy availability in blood, and corresponds to hunger sensation. The function is typically intermittent. In our observations, the frequency of hunger events increases with BG decline through hours. Yet by eating at scheduled mealtimes, adults tend to forestall the activation of the function for greater convenience. This convenient custom produces negative awareness. As regards energy intake, energy metabolism and immune activity (presence or not of a pro-inflammatory state), people think that consuming meals after hunger arousal is equivalent to scheduled intake. People even believe that appetite, i.e. the state of approaching offered food, coincides with hunger sensations. The customary approach to table may explain the unavoidable body weight increase as well as the large number of untrained people who declare to be hungry at breakfast (Figure 1). Hunger reports change and become clear cut after suggestion of stopping meals and waiting for hunger arousal (See training). However, there was the need to verify scientifically and demonstrate human capability of learning to recognize a subjective sensation like hunger by showing the association with the same biological state. We remind that blood glucose concentration (BG) is representative of total energy availability for body tissues because available nutrients are in mutual correlation and BG can substitute others. Additional factors give this representativeness to BG. Glucose is used before other nutrients, reserves are exhaustible, and utilization decreases with abundance of nutrients in all tissues. Thus, we assumed BG as representative of other nutrients in blood [17-19]. Within this view, nutrients provision, i.e. BG rise, is the aim for any meal. Stability of BG (homeostasis) at a level associated with minimal risks (neither high, nor at too low) is the scope of good nutrition. We now suggest observing Figure 1. Control subjects are representative of untrained population, ignoring intake and blood glucose problems. Part of them reported to be hungry and ready for breakfast despite of higher BG than trained people. Control subjects described hunger as tenuous, continuous state of hollow stomach rather than intermittent sensations of waves bursts like physiological studies suggest. Their statements reflected a lack of any kind of habit to self observation and in comparing present sensation to past experiences.

The investigation on initial hunger: In a 7-week pilot study, 158 adults suffering from diarrhea, abdominal pain, and dyspepsia were recruited and randomized to experimental (trained; n = 80) and control (untrained; n = 78) groups by the Pediatric Gastroenterology Unit of Florence University, a third level diagnostic center. Informed consent was obtained at the initial meeting from all the participants. The local Hospital Committee approved the study according to the Helsinki Declaration. The subjects did not have impaired glucose tolerance or morphological, physical, or biochemical signs of diseases. Reactive C protein was normal. Their diagnosis was functional bowel disorders [8,9,20-27]. We explained this disorder as a manifestation of insulin resistance and motivated training as a way to solve transient intestinal symptoms, in order to recover and indefinitely maintain insulin sensitivity, and to abate health risks. All subjects reduced work for 3-4 days at the beginning of the experiment and then conducted their normal routine. The experimental group was trained with tutorial assistance to a new meal. Meals were taken only after arousal of IH that is trained, validated hunger. This novel meal pattern had the name of "recognizing hunger" or "IH Meal Pattern (IHMP)".

After 7 weeks, 64 trained and 72 control subjects completed the program. In the final investigative session (week 7), they were asked to

estimate their glucose concentrations in the laboratory and these values were compared to those determined through a glucose autoanalyzer. BG measurements were reported on seven-day food diaries that were available before training and in the 7th experimental week.

Training to recognizing initial hunger: The fundamental action in training recognition the initial hunger (IH) began on the first day, and consisted of suspending food intake for hours, measurement of BG at earliest arousal of hunger sensation and memorization of the sensation [22]. Subjects identified hunger sensation after a mean of 2 hours from the first skipped meal. *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). (By kind permission of the Authors [22].

The range in watchful waiting was between 0 and 48 hours. At subsequent arousals (just before meal consumption), subjects in training checked the arousal in comparison with the memorized hunger to assess identity. Subjects validated their identity assessment by BG measurement. Identity of BG allowed intake. The moment of BG measurement was standardized to avoid deceiving conditions (See BG measurements). After 42 measurements at hunger arousal, the error of BG estimation, the difference from BG measurement, was significantly lower in trained than control, untrained subjects (Figure 1) [22]. Validated IH might arise earlier or later than planned time. Either delay or anticipation served to evaluate each previous meal as either excessive or scarce, and to compensate excess or scarcity [20,21]. Thus, the energy content was calibrated to a further hunger arousal before the planned, subsequent mealtime.

After 3-14 days of this training, subjects became aware of current BG state before meals by sensations [20-23]. After showing association with constant BG, we named the three sensations of epigastric hunger and of physical or mental weakness as "Initial Hunger" (IH). IH was maintained pre-meal, adjusting meal sizes, composition or timing of food intake. After a few days of trials and errors, and sometimes irregular mealtimes, subjects were able to arrange their intake so that IH appeared before the usual three mealtimes per day with an average error of half-an-hour in 80% of instances in adults and 90% in children (*recognizing hunger* or *Initial Hunger Meal Pattern, IHMP*) [8,9,20-23]. Thus, subjects chose the appropriate sensation of hunger with the associated BG the first day, and verified identity of sensation and BG

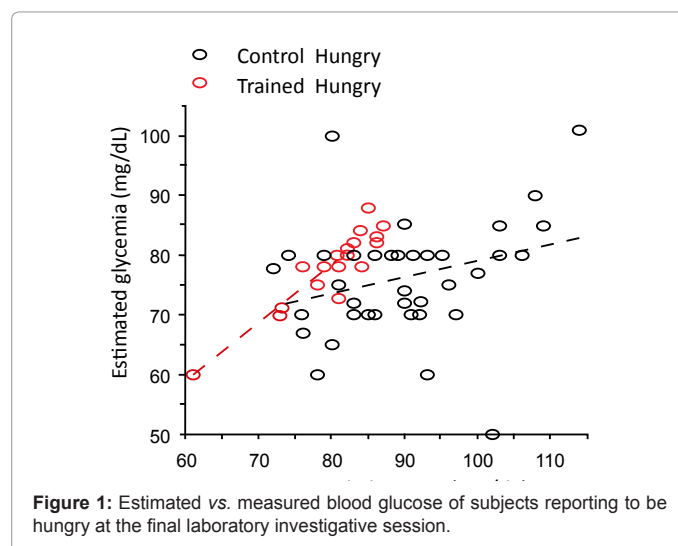


Figure 1: Estimated vs. measured blood glucose of subjects reporting to be hungry at the final laboratory investigative session.

at subsequent arousals. In subsequent days learned the food amount per meal, and confirmed the chosen sensation as reference for intake by showing the same low BG attainment (± 4 mg/dL) at each hunger arousal (before meal).

BG measurements: Subjects measured by themselves capillary blood by glucometer (a portable device for whole blood glucose measurement: Glucocard Memory; Menarini Diagnostics; Florence, Italy) within the 15 minutes before each meal. Accuracy of measurements by the glucometer was validated against periodic measurements by hospital autoanalyzer. Subjects avoided BG measurements taken less than 1 hour 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 being feverish, because BG in these circumstances is higher than 1 hour after cessation of the transient metabolic condition [22]. Seven-day home diaries reported BG measurements before the three main meal times, energy and vegetable intake, hours in bed and hours spent during physical and outdoor activities (weekly mean and SD) and presence or absence of preprandial sensation of epigastric hunger [8,9,22-25]. Subjects compiled the diaries before training, after seven weeks and at the end of investigation. Our previous studies include more details on validation of BG estimation compared to BG measurements; comparison of energy intake and total energy expenditure as assessed by doubly labeled water in infants [25]; HbA1c methods for anthropometric measurements, structured interviews, and relevant clinical blood tests.

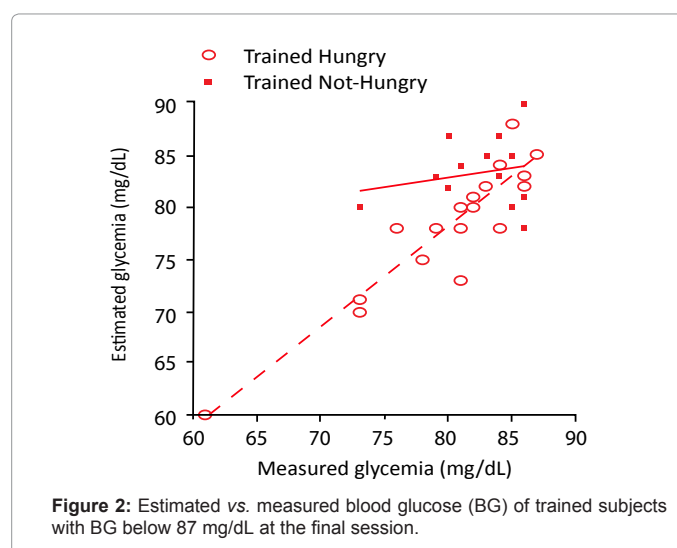
BG estimation by hungry subjects (gastric hunger) in hospital after 7 weeks training [22]: Sixty-four trained and 72 control subjects of 158 recruited adults arrived to hospital for the final session 7 weeks after recruitment. The number of trained subjects stating that they were hungry (18 of 64) was significantly lower than that of hungry control subjects (42 out of 72). All hungry subjects described the hunger sensation as gastric emptiness or gastric pangs. In the hungry trained group, the mean estimated glycemic concentration was 78.1 ± 6.7 and the mean measured value was 80.1 ± 6.3 mg/dL (Figure 1). 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 estimation error (the absolute value of the difference between estimated and measured glucose) in the hungry trained group (2.6 ± 1.9 mg/dL; $3.2 \pm 2.4\%$ of the measured value) was significantly lower than that in the hungry control group (14.9 ± 9.8 mg/dL; $16.7 \pm 11.0\%$). Linear regressions of the values in the hungry groups in (Figure 1) also show that there was significant correlation between estimated and measured BG in the trained group ($r = 0.92$; $p = 0.0001$) but not in the control group ($r = 0.29$; $p = 0.06$).

The highest BG measured in trained hungry subjects was 87 mg/dL. Below this value of measured BG, 18 subjects reported to be hungry (*hollow red circles*) and 14 subjects were not hungry (*filled red squares*). The errors in estimation (estimated BG value less measured one) showed no significant difference between the two groups. By kind permission of the Authors [22].

BG estimation by not-hungry (epigastric) subjects in hospital after 7 weeks training (hunger equivalents [22]: The trained and control subjects that were not hungry at the final investigative session significantly underestimated their glucose levels. The estimation errors were 4.8 ± 3.2 mg/dL and 16.1 ± 11.3 mg/dL in trained and control groups, respectively. The linear correlation between estimated and measured BG was highly significant ($r = 0.68$; $p = 0.0001$) in the trained group and not significant in controls ($r = -0.12$; $p = 0.32$). The difference

between trained and control groups did not depend on gender, age, number of years at school, weight, or body mass index. Fourteen out of 46 trained subjects who were not hungry had glucose concentrations below 87 mg/dL, the maximum limit of BG of those who were hungry (Figure 2).

These 14 subjects showed an average estimation error of $4.5 \pm 3.1\%$ of the measured BG, which did not significantly differ from the estimation error of the 18 trained subjects who were hungry ($3.2 \pm 2.4\%$; $p = 0.20$). Under 87 mg/dL, estimation error was low in both trained and control groups ($n = 32$; $3.8 \pm 3.7\%$ and $n = 31$; $13.5 \pm 8.9\%$ of the measurement, respectively), independently of the subject's statement on hunger. In subjects with values above 87 mg/dL of BG, the estimation error increased significantly to $5.7 \pm 3.7\%$ (trained; $n = 32$; $p = 0.04$) and to $19.5 \pm 11.8\%$ (controls; $n = 41$; $p = 0.001$). Despite their not being hungry, 12 of 14 trained subjects under 87 mg/dL and 3 of 32 above 87 mg/dL ($p = 0.001$) described the subtle sensations they employed to estimate glycemic concentrations. Thus, compared to controls - who did not report equivalents of hunger ($n = 30$) - a significantly higher proportion of the 46 not-hungry trained subject ($p = 0.001$) was able to report sensations other than gastric hunger, which were useful in estimating their glycemic levels, and this ability prevailed below 87 mg/dL. In their reports, these 15 subjects described physical (3 subjects) or mental [10] weakness or abdominal changes in tension or movement [2]. Another 6 of the 46 not-hungry trained subjects, but none of the control subjects, had felt gastric hunger before entering the hospital for the final session; however the sensation faded while waiting for the laboratory session. In the not-hungry subjects' 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 accompanied a change from a sedentary life style. This sensation was used regularly to indicate meal signal with an increased requirement of high energy-dense food for the next meal(s). The prevalence of these "hunger equivalents" ranged from an occasional occurrence to less than 15% of the meals in the phone reports. 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. In their reports, these subjects consumed meals at BG estimation of 78 to 85 mg/dL.

Overview on IH: Hunger is subjective and reports of being hungry may be unreliable, or more precisely may not coincide biochemically, metabolically and physiologically from a subject to another and from a report to another. After training, subjects became able to report with the term “initial hunger” (IH) the same sensation of insufficient provision of energy from blood to all body tissues. The condition of insufficiency was shown by low BG. We induced subjects with functional bowel disorders to use the signal of insufficiency in a novel meal pattern. The meal pattern was assessed by 7-day food-intake diary with BG standardized measurements before the three main meals. Mean weekly BG measures food intake as a mean provision of energy to body tissues at a metabolically standard time [20-25]. Thus, people may be compared by their habits in energy intake at the same metabolic moment. In our hypothesis, a mean weekly BG may be “desirable” if it is associated with loss of weight in both overweight subjects and insulin resistant subjects, and if insulin sensitive normal-weight subjects do neither increase nor decrease in weight. The desirable mean BG might be suggested by the associated risk decrease and not merely by the low level (LBG) in cross-sectional studies. Point 2 investigated these hypotheses.

Point 2: Effects of a meal pattern signaled by IH

Subjects: A controlled, randomized study investigated 181 adults three times in five months [20-24]. 59 were overweight (OW; BMI > 25) and 122 had functional bowel disorders (See, please, previous point 1). Subjects compiled the diary three times, at recruitment, after 7 weeks and after 5 months. 120 completed blood tests and diaries at recruitment and at the end of investigation, and provided information for the metabolic study. The anthropometry study included these 120 adults and further 29 overweight (OW) who compiled diaries but did no blood tests. Both control (N = 45) and trained (N = 104) subjects had the same information on food energy contents, on recommended vegetable intake and physical activity amount per day. The trained group exercised regularly under tutorial assistance for seven weeks, and maintained the new strategies of food consumption and energy expenditure for further three months without any assistance. The remaining 32 subjects (181 less 149) did not complete the 5 month protocol but they and their diaries were clinically assessed after 7 weeks.

Summary of findings by 7-day food-intake diary with BG standardized measurements

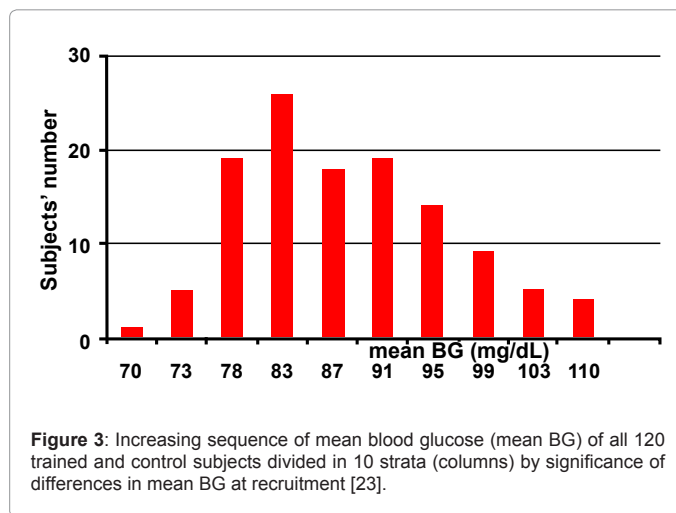
Metabolic study (120 subjects): At recruitment, 120 subjects were distributed in 10 mean BG strata [23]. Components of each stratum showed significantly different mean BG from components of other strata (Figure 3).

Control, untrained subjects maintained constant mean BG over 5 months, the absolute change being 6.0 ± 4.6 mg/dL [23]. Trained subjects split in two groups at recruitment in response to “recognizing hunger”. Low mean BG subjects (LBG, < 81.8mg/dL) were insulin sensitive and showed no response in mean BG, body weight and other parameters [23]. *Recognizing hunger* (IHMP) significantly decreased high mean BG, energy intake, HBA1c, body weight and few signs of metabolic syndrome, and increased the indices of insulin sensitivity and of beta cell function in OW subjects and in those NW subjects who were HBG (> 81.8mg/dL). Forty-one of fifty-five HBG adults did not differ in mean BG and metabolic parameters at the end of the investigation from LBG subjects at recruitment.

In every investigated group, we always found some subjects

maintaining LBG by free choice before any training, and obviously many subjects who acquired LBG after training (Table 1).

The associations of LBG with insulin sensitivity and of HBG with insulin resistance confirm earlier controlled, randomized studies in which we adapted *Recognizing hunger* to infants by substituting *Initial Request* of children for *Initial Hunger* of adults (*Initial Request Meal Pattern*, IRMP) [8,9]. Daily activity was preserved and body weight increased normally in children with chronic non-specific diarrhea (functional bowel disease in infancy) after seven months, 4 years and 12 years of complying with IRMP [8,9,26,27]. In 73 infants [25], the most significant cutoff divided subjects with low mean BG at 81.2 mg/dL from those with high mean BG at recruitment. By this division, 18 infants showed low mean BG and 55 infants showed high mean BG at recruitment. This cutoff in infants is quite similar to the cutoff (81.8 mg/dL) that we found in adults in the present report and to the cutoff found in prevention of non-insulin dependent diabetes in Israeli recruits [28]. In a longitudinal investigation of 13,163 subjects a fasting plasma glucose of ≥ 87 mg/dL (4.8 mmol/l) was found to be associated with an increased risk of NIDD in men compared to those whose fasting plasma glucose was < 81 mg/dL, (4.5 mmol/l).



Training 1	Before	After
34 adults (BMI from 17 to 40) ²	76.6 ± 3.7	77.2 ± 4.2
12 adults, ctrl ²	76.9 ± 3.4	No training
18 diarrheic infants	77.1 ± 3.8	75.2 ± 6.9
9 normal-weight adults, ctrl	77.3 ± 3.9	No training
26 normal-weight adults, ²	76.5 ± 3.9	76.7 ± 4.1
8 overweight adults, ctrl	77.4 ± 3.6	No training
12 overweight adults	77.1 ± 3.1	77.2 ± 4.8
41 HBG adults ^{2,3}	91.7 ± 7.8	78.5 ± 6.8
41 HBG infants ⁴	92.3 ± 7.7	74.7 ± 5.1

¹Trained subjects show mean BG both before and after training. No training refers to subjects kept as control (ctrl).

²Mean ± SD of mean diary of 21 preprandial BG in a week in mg/dL, present investigation, subchapter 2.

³41 of 55 adults with mixed body mass index (BMI) and mean BG > 81.8 mg/dL at recruitment who significantly decreased mean BG after training “recognizing hunger”.

⁴41 of 55 HBG infants of 73 recruited because of chronic diarrhea, who showed arm skin-fold thickness on 15th percentile of normal reference. They significantly decreased mean BG from > 81.1 mg/dL the level at recruitment. Further 18 of 73 diarrheic infants appear in the third line.

Table 1: Occurrence of low mean blood glucose (LBG) either by free, spontaneous choice (Before) or after training (After) “recognizing hunger” in 9 different groups

In the same preliminary work [25], we reported a significant 15% - 16% decrease in RMR by respiratory calorimetry and in total daily expenditure (TDE) by doubly labeled water in 24 infants from before training to during IRMP. IRMP decreased mean BG, RMR and TDE in infants. We are interpreting the three decreases during IRMP (Vs. meal pattern at recruitment) as an elimination of forestalling IH, i.e. leaving behind meal by meal positive balance and acquiring null balance in blood. Taking together the investigations on children and adults [8,9,20-27], recognizing hunger decreases mean BG, HbA1c, RMR and TDE, meal by meal positive balance in blood, insulin resistance, functional bowel disorders, and vascular risks (*subclinical inflammation*). "Recognizing hunger" shows occasional lower intake than expenditure as for example during psychological stress or fever, but the transient deficits are regularly compensated within few days. Negative energy balance was prevented in the 5 month study [23].

Body weight study (149 subjects) [21]: Thirty-two of 181 subjects dropped out after 7-weeks. Their clinical data and the diary assessments confirmed results obtained in 149 at the end of the investigation [21].

Our results showed substantial weight decreases at study end not only in OW subjects but also in many NW subjects. It appeared that those NW subjects with high baseline BG might account for most of the weight loss shown by NW subjects. It was of interest therefore to use the "cut-off" value (demarcation point) of mean BG concentration that most significantly divided HBG and LBG subgroups in the previous metabolic study (81.8 mg/dL) to set apart four subgroups:

two subgroups (OW and NW) with low baseline BG (LBG) and two subgroups (OW and NW) with high baseline BG (HBG). Similarly, the BG value of 81.8 mg/dL was used to divide control subjects into OW and NW LBG and HBG control subgroups.

In LBG NW and OW subjects (mean premeal BG < 81.8 mg/dL; n = 26 and 12) mean premeal BG remained constant after training, whereas in HBG NW and OW subjects (mean premeal ≥ 81.8 mg/dL; n = 40 and 26) mean premeal BG significantly decreased. The longitudinal difference was significantly greater than in the control subgroups. In the control subgroups, the BG did not decrease during the study time interval in any of the four subgroups.

The pre/post decreases after training in mean premeal BG, diary-BG SD, energy intake, body weight, body mass index (BMI), arm and leg skinfold thickness were all significantly greater in the trained NW HBG subgroup than in the corresponding control subjects (Table 2). In the metabolic study, trained NW HBG subgroup was insulin resistant at baseline and significantly improved insulin sensitivity after training. These facts suggest that mean HBG and insulin resistance are markers of an overweight state below 25 of BMI.

Mean premeal BG, diary-BG SD, body weight and BMI decreased significantly in OW HBG trained subjects compared to controls. Control OW HBG subjects also showed a significantly lower energy intake, body weight and BMI (Table 2), but not mean premeal BG, at investigation end compared to baseline. The discrepancy prompted us to analyze energy intake, BG and body weight at 7 weeks of

Normal-Weight	Low BG group		High BG group					
	Control	Trained	Control	Trained				
	Baseline	After 5 mo.	Baseline	After 5 mo.	Baseline	After 5 mo.	Baseline	After 5 mo.
Energy intake ¹	1794±587	1660±732	1518±586	1357±628	2034±528	1886±417	1852±697	1270±457 **,a***,b
BG group mean premeal ²	77.3±3.9	79.8±3.7	76.5±3.9	76.7±4.1	90.7±5.2	89.7±6.6	91.4±7.7	80.1±6.6 ***,a***,b
Diary BG SD ²	8.0±2.4	9.1±1.7	6.3±3.0	5.2±1.8 **,a*,b	8.6±2.2	8.5±2.4	9.1±3.9	6.6±2.5 **,a***,b
BMI ³	20.3±1.7	21.0±2.8	21.1±1.8	20.7±1.6	20.2±2.3	21.4±2.1	21.8±2.4	20.7±1.9 ***,a***,b
Weight ⁴	55.2±7.7	57.0±9.6	57.9±7.8	57.0±7.6	57.5±6.9	60.9±6.4	61.4±10.4	58.9±9.6 ***,a***,b
Arm skinfold thickness ⁵	12.9±5.3	14.7±7.7	12.6±6.6	11.3±5.0	11.3±4.3	11.7±4.2	14.1±7.0	11.6±5.7 **,a***,b
Leg skinfold thickness ⁵	17.9±8.7	18.6±11.0	17.6±9.3	15.9±7.7	16.0±6.6	15.6±6.5	20.4±10.3	16.2±8.4 **,a***,b
Over-Weight								
Energy intake ¹	1611±471	1257±629	1618±616	950±448** _{,b}	1799±701	1343±489 *,b	1820±570	1123±503 ***,b
BG group mean premeal ²	77.4±3.6	81.8±6.9	77.1±3.1	77.2±4.8	90.9±7.1	93.9±4.8	91.3±6.5	79.6±7.5 *** _{,a***,b}
Diary BG SD ²	9.1±4.5	8.2±2.6	7.9±2.9	4.8±2.0 ** _{,b}	8.7±4.2	9.4±4.5	10.4±5.4	7.1±4.0 **,a** _{,b}
BMI ³	29.1±7.9	28.9±7.6	27.9±2.0	26.5±1.9 *,a*** _{,b}	29.2±3.9	27.8±4.2 *,b	29.0±4.1	26.5±4.0 *,a*** _{,b}
Weight ⁴	74.5±18.3	74.1±17.9	77.0±9.5	73.0±9.1 *,a*** _{,b}	77.1±16.2	73.7±15.9 *,b	78.5±10.6	71.8±10.7 *,a*** _{,b}
Arm skinfold thickness ⁵	25.3±10.8	23.3±8.7 ** _{,b}	25.9±7.0	21.8±6.4 *,b	25.5±9.9	19.6±6.8	25.7±10.2	19.09±8.2 *** _{,b}
Leg skinfold thickness ⁵	33.7±13.7	30.3±12.6 ** _{,b}	32.5±12.1	26.6±10.3 *** _{,b}	34.9±13.1	29.4±9.8** _{,b}	31.9±13.1	24.4±10.3 *** _{,b}

¹Kcal/d. ² mg/dL; diary SD refers to BG SD of 21 measurements reported by each of 7d diary. ³body weight kg/square height meters. ⁴Kg. ⁵mm. Asterisks indicate significant differences (Student's t-test or Yates test: *, P < 0.05; **, P < 0.01; ***, P < 0.001) vs. respective control group values based on "post – pre" measurements (a), or vs. baseline values of the same group (b).

Table 2: Effects of training (IHMP) on diary reports and anthropometry in normal- and over-weight groups divided by low and high mean premeal BG.

investigation. At 7 weeks, daily energy intake was 1082 ± 290 kcal/d and BG 88.0 ± 6.2 mg/dL in control OW HBG subjects. The two values were significantly lower than at investigation end ($n = 13$, $P < 0.02$ and 0.01). At 7 weeks, body weight was 72.8 ± 15.3 kg which was significantly lower than at baseline ($P = 0.0001$) but did not differ from study end. Control subjects were encouraged to lose weight and can be considered to represent a conventional restraint approach to dieting. Although control OW HBG subjects significantly lost weight in the first two months they significantly increased their energy intake and BG during the last three months of the study and lost no further weight. This is consistent with a “restrained” eating pattern.

In the NW LBG group, only the decrease in diary-BG SD was significantly greater than in control subjects in the longitudinal comparison after training. In the OW LBG group, the training was associated with significant pre/post decrease in energy intake, diary BG SD, BMI, body weight, arm and leg skinfold thickness, and the decreases in body weight and BMI were greater than in the OW LBG control group. Moreover, trained OW LBG subjects showed significantly lower energy intake per meal and lower number of meals per day (279 ± 128 kcal per 3.4 ± 0.6 ; $n = 285$ meals, $P = 0.001$) than NW LBG subjects (367 ± 116 kcal per 3.7 ± 0.7 ; $n = 673$ meals). HBG NW and OW subjects showed no such differences after training [21]. Control OW LBG subjects showed a mean premeal BG just at 81.8 mg/dL at the end of the study indicating that without training, their meals remained partly conditioned, thus explaining firstly, their overweight status, and secondly, their failure to lose weight. Thus the training appeared to decrease weight in OW or HBG subjects while NW LBG subjects maintained normal weight. The findings in the two control OW subgroups (LBG and HBG) are consistent with the fact that restraint-type dieting tends to give short term results that are not sustained.

Point 3: Amount of energy intake per meal

Energy intake had to cover only the needs for activity in the interval between meals and not for a longer period (*Initial Hunger Meal Pattern or recognizing hunger*). This statement seems obvious, yet few people (38%) took it as a table guide at recruitment. A large body of studies report that a positive energy balance is associated with development of insulin resistance. Resistance damages all tissues and increases immune, tumor and cardiovascular risks by increasing antigenic stimulation of the small intestinal mucosa and producing a subclinical inflammation (pro-inflammatory state) throughout all the body.

The small intestinal mucosa hosts half body production of immune cells and antibodies that locally counteract adherence and invasion of antigens into the body. Epithelial cells and monocytes (dendrocytes) orchestrate initial reaction. Studies on germ free animals suggest that about 90% of the immune defense is against microbial antigens [29-39]. Ten grams of IgA (10^{17} molecules) come into the small intestine every day. Forty percent bacteria are immunogenic and evoke IgA response, 15% more destructive responses by IgM, IgG and complement activation and activated oxygen [29-32]. Immunogenic bacteria have modest pathogenic power on small intestinal mucosa and on all body in comparison with frankly pathogenic bacteria like *Yersinia pestis* or salmonella species. Mucosal immune reaction rapidly devitalizes immunogenic bacteria, but fragments persist in immunocytes, VLDL and LDL, blood and lymph circles and invade all the body [31,32,39-41]. The inflammatory stimulation by bacteria, i.e. immune activation, extends to vascular endothelia, liver, joints, heart, kidneys, bronchial mucosa, skin and all body organs [29-40]. Lipopolysaccharides (LPS, endotoxins) represent a third of the weight of Gram negative bacteria,

100 trillion in the colon that might locally produce 10-30 grams of LPS every day. A variable part gets into the blood circle [33]. The passage increases with mucosal inflammation. Endotoxins contain muramyl peptides that have the capacity to give direct rise to an immune response. We hypothesized that immunogenic bacteria might grow in nutrients remaining in the small intestine for few hours. Representing a conspicuous part of all bacteria in the alimentary canal (10% - 40%), we may think that immunogenic bacteria spp. is always available to grow in the small intestine. Health might consist in the persistence of low numbers by intake of food amounts that are rapidly absorbed.

Microbiological investigations: We developed a procedure to sterilize the Watson biopsy capsule with HCl in the upper portion of the duodenum [42]. We counted bacteria in the mucosal homogenate of the first (diagnostic) duodeno-jejunal biopsy in 80 untreated celiac children, and in 46 children with irritable bowel syndrome (IBS) in a four-cell, controlled, randomized investigation. Persistence of bacteria on the mucosa for 20 h after the last meal was investigated in 62 subjects and for 26 h after the last meal in 64 subjects. Bacteria, mainly streptococci and staphylococci, persisted at a concentration of 10^6 per gram of mucosa 20 h after the last meal. The number of bacteria per gram of mucosa was 24 times higher in all 62 children of the 20-h fast groups than in all 64 children of the 26-h fast groups ($p < 0.001$). The bacteria count in celiac children was 39 times higher in the 20-h fast group than in the 26-h one. This difference was significantly higher than the 11 times difference that was found on the normal mucosa between the 20- and 26-h fast IBS groups ($p < 0.001$), which was still significant. The number of bacteria on duodeno-jejunal mucosa depended on nutrient absorption, diminished slowly and persisted longer than the inter-meal interval in the investigated subjects who were well and capable of usual physical activity but convalescent at medical evaluation, i.e. in a state of insulin resistance [41].

Nutrient flux in small intestine may sustain a doubling of bacterial number every 20 minutes. Within three hours the number may increase by 1000 times, and symmetrically decrease in subsequent hours. We might desire a completion of absorption in 2 or 3 hours. A recent paper confirmed the role of energy-rich food inside the alimentary canal [43]. In feces, firmicity bacteria and energy loss increased, and bacteroides decreased in proportion to the meal energy administration. Thus, insulin resistance slows absorption and promotes immunogenic bacterial growth, immune stimulation of intestinal mucosa, and development of subclinical inflammation (proinflammatory state) in all tissues [40,41].

Adaptation of energy intake to expenditure between subsequent meals: In the first days and months of life, request for food may be satisfied if three hours passed from the previous meal. In the second year of life, infants find food everywhere at home and ask for it. The best policy might be to keep them playing outdoors. Lack of this resource obliges mothers to identify arousal of hunger from small signs and changes in behavior. We investigated 30 adolescents by 7-d diary with preprandial BG measurements in a high school of Florence. They had information on the importance of hunger from their brief physiology course at high school and not from medical advices. Twenty-five of thirty showed a mean BG of 76.3 ± 4.6 mg/dL and the other 5 showed 84.9 ± 7.1 mg/dL. From these results we can at least infer that adolescents can easily recognize IH. Results also suggest that the ability deteriorated toward the age of 33 years old (Table 2, point 1).

“Recognizing hunger” largely coincides with LBG meal patterns. The point of mean inversion from HBG was at 81.8 mg/dL. However, 27 out of 89 trained subjects (metabolic study) further persisted at

HBG level at final investigation after completion of 5 months study. Fifteen out of 27 were within LBG limits after seven weeks training and their HBG regression was explained by fading of trained instructions in the last three investigated months. Six of the 27 subjects were engaged in heavy handwork during cool winters. The six subjects had a mean BG of 86.4 ± 4.0 mg/dL that showed no difference from 87.1 ± 5.3 mg/dL in 21 out of 27 other subjects. IH developed in these heavy outdoor workers at higher levels than 81.8 mg/dL. This conclusion is sustained by the significantly higher insulin sensitivity in the six outdoor heavy workers than the other 21 subjects (Table 3). Subjects engaged in intense physical activity may require HBG for high energy expenditure. The division between compliance and no compliance with “recognizing hunger” is statistically strong at 81.8 mg/dL, but subjects who have high energy expenditure and actually comply with “recognizing hunger” may show higher mean BG than 81.8 mg/dL, an overlapping over HBG [23].

The mean BG from 7-d diary is a measure of individual energy provision to body tissues and an indication of either insulin sensitivity for mean LBG or insulin resistance for mean HBG (See point 2). In the high school investigation, 25 of 30 young adolescents had low mean BG that was appropriate to maintain insulin sensitivity. Other 5 adolescents showed a mean BG of 84.9 ± 7.1 mg/dL, and might either have high energy expenditure and insulin sensitivity or low energy expenditure and insulin resistance. Definitive information on this point might be provided by glucose tolerance test (GTT).

Age increase is probably associated with an increase in the error of BG estimation. The metabolic investigation on 120 subjects at recruitment showed higher mean BG at the age of 33 years old than that on 30 subjects at the age of 18 years old. A limited investigation on 12 untrained subject’s over-60 demonstrated a significant ($P < 0.05$) increase in estimation error in comparison with 34 lower age subjects.

Measures of high energy intake: The gold standard for quantifying insulin sensitivity (and resistance) is the “hyperinsulinemic euglycemic clamp” so-called because it measures the amount of glucose necessary to maintain BG at constant level after increase of blood insulin at constant level by i.v. infusion. If high levels of glucose (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. The glucose tolerance test (GTT) measures BG and insulin plasma levels for three hours after 300 kcal of oral glucose. A mathematical formula takes into account the elevations of BG and insulin to calculate an index of insulin efficiency [44] and the index of beta cell function [45]. BG represents instant balance between influx and efflux of nutrients from blood. Preprandial BG and preprandial insulin show energy balance meal by meal. The two measurements are used together in the denominator of HOMA estimate ($22.5/BG$ in mmol/L multiplied by plasma insulin in microU/mL). HOMA is considered an estimate of insulin sensitivity [46]. We consider HOMA as the best (inverse) estimation of meal by meal energy balance in blood: high HOMA suggests negative balance and low HOMA suggests a positive balance from previous meal. Meals are habitual, and low HOMA suggests insulin resistance development. Mean BG before meals is an assessment of (habitual) intake in the provision of energy to body and in the maintenance of insulin sensitivity, over being useful in training and in training assessment [20-23]. We used mean BG in a week, HbA1c, fasting insulin, index of insulin resistance from GGT as measures of excess energy availability. Each measurement may change in time and changes are correlated. Rapidity of change is different for each measurement.

Diabetes treatment: In this research, “Recognizing Hunger” prevented insulin resistance and non insulin dependent diabetes

(NIDD) in young, clinically healthy, subjects with “normal” BG. The aim was suppressing subclinical inflammation (pro-inflammatory state) and the associated functional disorders and evolving vascular diseases [30-32,39-41]. “Recognizing hunger” might be helpful also to some people with NIDD. Unfortunately, “Recognizing hunger” contrasts the currently prevailing idea of constancy in time of daily energy intake. NIDD patients may have no hunger sensation at all. Absent arousal of hunger yet facilitates low energy intake. As an extreme example, two meals per day of 50 grams of fish and salad, 100 kcal per meal produced rapid and large weight loss and recovery of hunger sensations after adequate weight loss. Some of these lowered weight people may show low estimation error of BG after training “Recognizing hunger” [22]. The low error validates “Recognizing hunger”, and prevents regaining body weight [21]. Thus, adaptation of “Recognizing hunger” to treating aged people with fully developed NIDD requires further investigation, and suggests that current treatment practices shall survive for part of patients.

Point 4: Contingent factors affecting a clear cut arousal of IH. Environmental temperature and humidity, physical activity, lean body mass, training, content of previous meal (like vegetables, fruits, fats, type of fats and proteins), emptiness of small intestine at meal onset, age over 60

Most statements in this Point 4 are observational as well as few statements in previous points. We demonstrated up to now that adaptation of intake to IH arousal decreased mean BG, insulin resistance and, obviously, the associated subclinical inflammation throughout all the body. This achievement is scientific and reproducible by humans of good will. In this accomplishment, we intended to give subjects freedom in choosing the way of adaptation and of acquiring more and more experience in “recognizing hunger”. On the other hand, we might be helpful with our experience also in choosing adaptation. This is the aim of present Point 4 in reporting mainly observations. An observational statement may become a scientific rule or a neutral or dangerous prejudice after ad hoc investigation.

The meal by meal dynamic balance of energy: The yearly or monthly steady balance is insufficient to guarantee nutritional health because it ignores weight wavering and periods of excessive energy availability. Insulin sensitivity and suppression of subclinical inflammation (pro-inflammatory state) is associated with mean BG, i.e. with current energy intake and not with body weight [23]. The energy provision includes glucose, fatty acids and amino-acids and is the scope and consequence of meal intake. Available nutrients are in mutual correlation and blood glucose (BG) can substitute others.

	6 HBG 1	21 HBG 2
Mean Blood glucose (mg/dL)	86.4 ± 4.0	87.1 ± 5.3
Final insulin AUC (mU L-13h-1)	124 ± 26	207 ± 99 **
Final blood glucose AUC (mg dL-13h-1)	536 ± 56	601 ± 82 *
Insulin Sensitivity Index	11.4 ± 2.9	6.68 ± 4.0 ***
Beta cell Function Index	1.29 ± 0.66	1.43 ± 1.22

Values are expressed as means \pm SD. Asterisks indicate a significant difference (Student’s t-test: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$)

of 6 HBG subjects from the other 21 of 27 HBG subjects at investigation end.

*Six HBG subjects reported to make heavy handwork all day in outdoor environment during cold winter and to practice “recognizing hunger”.

No significant differences in the five parameters from recruitment. At recruitment mean BG = 86.9 ± 5.3 mg/dL.

*21 HBG subjects included 15 that were LBG after seven weeks training (at clinical assessment) and six who had higher mean BG than 100 mg/dL at recruitment.

Table 3: Effects of heavy outdoor work1 in 27 trained subjects who remained with high BG at investigation end.

BG is used before other nutrients, reserves are exhaustible, utilization decreases with an abundance of nutrients in all tissues. We used BG as representative of other nutrients in blood [17-19]. Thus, nutrients provision, i.e. BG rise, is the aim for any meal. Provision to body cells consists in the instant concentration of macronutrients and in their energy content. Provision depends on instant balance between entry and efflux of nutrients in the blood. This balance is dynamic like a flux in a tank with a tap that provides the input at intervals and with a permanently open exit. Blood contains about 6-7 grams of glucose; thus, the meal is mostly stored in a transient container produced by insulin release during the meal and after the meal. Instant balance and instant provision consist of BG value. Meal by meal dynamic balance of energy is much more important and consists of BG value before further energy addition, before meal consumption. At this time, the level of nutrients and glucose in blood results from balance in blood between entry (previous meal intake and fatty acids release in blood from adipose tissues and aminoacids from muscles) and exit (expenditure plus fatty acids deposition) in previous inter-meal interval, according to our findings [20-27]. Somebody might suggest that inter-meal balance is positive when the second preprandial value (before lunch) is higher than the first (before breakfast). Yet, balance is positive all the times it is associated with energy accumulation. Meal by meal balance is thus positive when preprandial BG is high, even if it is constant. Meal by meal balance is negative when meal energy plus influx from adipose tissues is lower than expenditure. In this case, preprandial BG is very low. Meal by meal balance is often null and BG is just low (LBG). Meal by meal energy balance in blood (BG) coincides only approximately with body energy balance in the interval between meals. Instead, we found a close correlation between the habit in null meal by meal energy balance in blood and no body weight increase or decrease in lean, insulin sensitive subjects in a period of five months [23]. Mean preprandial BG measured habitual meal by meal BG balance in blood and body weight measured body energy balance in a time period. For health purposes, achievement of null energy balance in blood through days and weeks is more effective than a precisely null meal by meal body energy balance. E.g., fever increases energy expenditure and requires a decrease of body weight to recover [47]. Psychological stress may not change expenditure, but the associated high BG requires no intake by maintenance of “recognizing hunger”, and a healthy, transient body weight loss. Meal by meal null balance in blood is an effective tool in the achievement of long term healthiest body functions and weight. A healthy hormonal function might even develop the most attractive body. Achievement of null balance is difficult, but rather more common than expectation. Small physiological adaptations in intake time or amount, or in expenditure, deliberate or unconscious, allow frequent achievement of null balance. This research might help in focusing attention on this achievement and related factors. Adapting intake to IH arousal requires learning personal responses to intake and consuming foods in amounts to strictly cover the foreseen time interval. Like most human activities requires more attention and more know how than pain.

The first dilemma we encountered was either maintaining scheduled meals or accept intake after free arousal of hunger at any hour of the day. The vast majority adapted intake to customary mealtimes. Only few disordered families adopted variable mealtimes. Either one IH arousal per day or even every two days might be better than three times a day? Overweight (OW) subjects differ from normal-weight (NW) subjects in higher insulin production and higher adipocyte proliferation. High insulin and high cortisol collaborate in adipocyte number increase and prompt response to nutrients in blood [48]. Subjects with this hormonal profile efficiently allocate bigger meals than NW people. This is the reason of their fattening. High insulin production might allow more rapid intestinal meal absorption than low insulin production in lean subjects. There are examples in carnivores with two habitual meals per week. We observed contrasting responses in glycated hemoglobin between thin and fat subjects after eating big dinners, sufficient for sixteen hours of sleeping and activity without breakfast. Fat subjects decreasing body weight were able to maintain lower HbA1c than NW subjects who increased their weight. Consuming two meals per day, OW subjects might more easily maintain LBG, low glycated Hb and high insulin sensitivity than NW subjects. (Table 4) confirms this trend. Every meal is a solicitation to food intake by release of insulin and ghrelin from the very beginning [49]. However, our concern for further decrease in meal number per day is that a release of fatty acids from adipose tissues has a tighter gate than the influx. This may mean long hours of physical weakness and bursts of intense hunger and the meal pattern becomes not durable. Moreover, enduring one meal per day may become risky for occasional errors: food may enter into a small intestine with a basal number of bacteria on mucosa as high as around 100 million per gram. The bacteria growth issue has a background dilemma: is it sufficient eating at IH arousal or we may better improve health by achieving small intervals between IH arousals (meals)? After years of doubts we concluded that intervals between IH must be short. Purpose of any meal might be rapid absorption, 2 to 3 hours (See also point 3). Small meals, about 100 kcal lower than expenditure [21] seemed a good solution for weight decrease. Maintenance of high expenditure by outdoor physical activity may make easier short intervals. Lean body mass is responsible for 75% of energy expenditure and is increased by physical activity, which in turn also increases energy expenditure.

Limitation of meal energy content has been addressed by most scientific works. People may have different lag phase between intake and satiety. Infants require about a quarter of an hour from early intake and satiety, and this lag phase remains rather constant through ages. A habit to small mouthfuls and long mastication should patiently be enforced from childhood. A customary distraction from table might also be patiently elaborated to stop intake when sufficient. Sedentary life requires low intake that becomes difficult with no fruit and vegetables. We suggest intake of copious amount of these foods to prolong intake until satiety. Physical activity and high vegetable intake

Categories	Subject Number	Breakfast		Lunch & Dinner		Number of meals per day ²	
		Yes ¹	No ¹	Yes ¹	No ¹	Before	After ¹
6-18 Normal-weight	27	397 (77%)	117	959 (82%)	212	4.39±0.61	3.92±0.67 ^b
6-18 Overweight	16	148 (65%) ^a	78	377 (76%) ^a	117	4.40±0.75	3.71±0.69 ^b
>18 Normal-weight	17	211 (71%)	86	647 (90%)	73	3.85±0.75	3.59±0.77 ^b
>18 Overweight	32	364 (67%)	182	1013 (77%) ^a	297	3.72±0.70	3.46±0.67 ^b

¹Number of diaries after training. Validated IH reported in 7-d diary.

²meals are: breakfasts, lunches, dinners and snacks with a caloric content > 20 kcal.

^aP < 0.01 vs. normal-weight subjects of same age group.

^bP < 0.001 vs. recruitment

Table 4: Number of meals induced by initial hunger in four trained groups.

also contribute to a positive balance of minerals and other nutrients. Colon fermentation may arrive to cover 600 Kcal, an amount sufficient for life in bed. Vegetables and fruits cover the final inter-meal hours by products of fermentation, and tend to delay and smooth emergence of IH by this fermentation. When IH develops too slowly, we have to avoid an excessive fruit and vegetable intake. Also fats and proteins may delay IH arousal and decrease its intensity in dependence on late utilization after intake. Storage of fatty acids differed between classes: n-3 < saturated < n-6 < monounsaturated [50,51]. Non-fat nutrient oxidation rates rise and fall to match the fluctuations in non-fat intake so that non-fat calorie balance is actively maintained. In contrast, changes in fat intake do not acutely affect fat oxidation but are matched by changes in storage. Therefore, within the fat balance equation there is ample scope for a chronic imbalance between fat intake and oxidation.

Energy expenditure is unfortunately highly variable, variations up to 20 times are well known, but might be higher. High environmental temperature and high humidity depress energy expenditure and intestinal absorption [52-54]. An increase in winds, a change in living rooms or environment may easily increase or decrease expenditure by a quarter. Outdoor physical exercise may double expenditure throughout the between meals interval. Training and large lean body mass reinforce environmental differences. An intake that fits for all people or for all days does not exist. Arousal of IH depends on energy balance in the previous few hours, and more precisely, on dynamic energy balance of energy in blood. Venturing meal by meal balance requires attention and experience. We trust less on occasional compensation by increase in physical exercise. The compensation by this way may reach 50%. Dietary induced thermogenesis [25] may increase or decrease expenditure by 15%; meals can be delayed or reduced in content. At recruitment, a third of investigated subjects maintained null balance in blood by personal untrained choices.

Conclusion

As regards effects on energy intake, BMI, body weight and fattening, mean BG, HbA1c, indices of insulin sensitivity and of beta cell function this review rejects the null hypothesis between a meal pattern based on scheduled meals and a meal pattern based of *recognizing hunger*. The review provides the know-how to revert meal pattern to three initial hunger arousal per day.

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