23

"Recognizing Hunger" – A Training to Abate Insulin Resistance, Associated Subclinical Inflammation and Cardiovascular Risks

Mario Ciampolini
Università di Firenze,
Italy

1. Introduction

1.1 Background

People cannot share subjective sensations with others as they do with sounds and figures. Subjective sensations guide the intake. In this chapter, subjective sensations of hunger that induce intake, become objective (verifiable by others, reproducible and comparable) by the association with measurements of blood glucose concentration (BG). This is possible after about two weeks of training with BG measurements. Subjective sensations become thus a meal by meal information tool on energy balance. Respecting the arousal of the validated sensation before any intake was useful to treat infants with chronic non-specific diarrhea (Ciampolini et al. 1990). In a health policy for cardiovascular risk prevention, for a suppression of subclinical inflammation and for a decrease or maintenance of a stable body weight, treating functional intestinal disorders means treating a reversible condition like insulin resistance to prevent irreversible events. Functional intestinal disorders are also capable to give valid motivation to patients for training (see further "Training to...").

Subjective signals that promote intake are reported by many researchers (Harshaw, 2008). In past investigations, we suggested subjects to find a subjective target (initial hunger, IH) before intake on the first day, and measuring blood glucose concentration as a marker of this target on the first and subsequent days (Ciampolini & Bianchi, 2006a).

In our experience, less than 10% of healthy people report never perceiving any kind of hunger. No perception may depend on insulin resistance or non-insulin dependent diabetes (NIDD). With the word hunger, all over the world, healthy subjects report gastric pangs or sensations of gastric emptiness. In other circumstances, the subject's definition is inadequate. Subjects trained to "hunger recognition" were able to assess current value of blood glucose with a fairly low estimation error from measurement (Figure 1) both when they either recognized or denied hunger (Figure 2, Ciampolini & Bianchi, 2006a). Subjects who denied hunger, reported mental and/or physical sensations of weakness. They reported these sensations from 10% to 45% of instances of eating induction. In these instances, animals actually show a decrease of resting metabolic rate (RMR). In this report, with the term "initial hunger" (IH) we indicate gastric, physical and mental sensations that are associated with a low error of estimation of BG measurement after training (Ciampolini & Bianchi, 2006a).

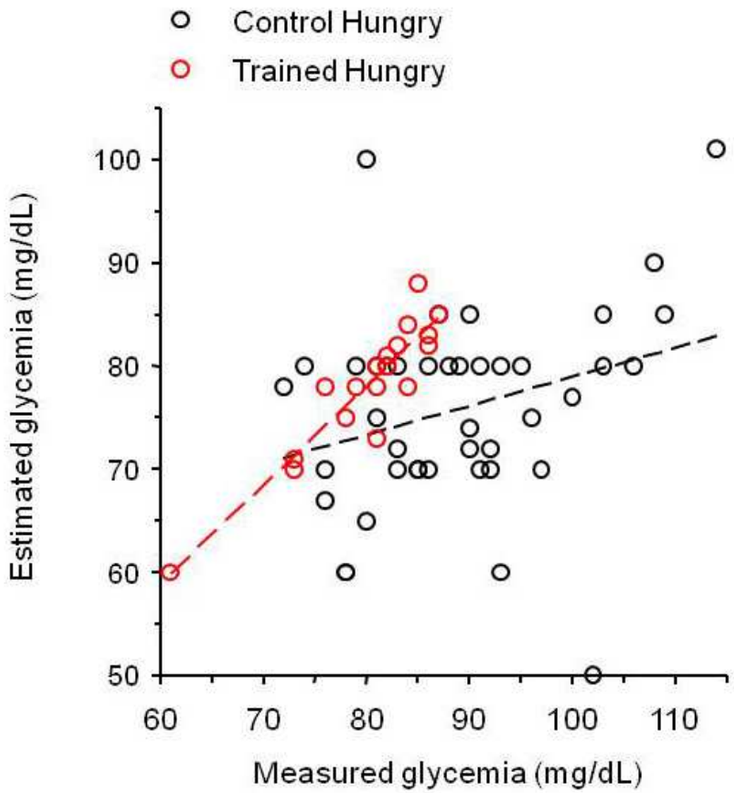


Fig. 1. Estimated *vs.* measured blood glucose of subjects reporting to be hungry at the final laboratory investigative session.
Hollow red circles, trained hungry subjects (n = 18); hollow black circles, control (untrained) hungry subjects (n = 42). Linear correlation was significant for the trained 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: Ciampolini & Bianchi, 2006a).

We named intake adaptation to IH arousal before meals three times a day as initial hunger meal pattern (IHMP) (Ciampolini et al. 2010°; 2010b; Ciampolini & Sifone, 2011). This is a meal pattern based on "recognizing hunger". We use these two simple words in this report to be more evocative than by using the term IHMP. We chose the assessment of the validated sensation and of BG measurement before meals for six reasons: first, because before meals people sometimes recognise definite hunger sensations, and are able to validate them through BG measurement (Ciampolini & Bianchi, 2006a). Second, a BG measurement (as well as validated hunger sensations, initial hunger, IH) is an evaluation of either sufficiency or excess of energy intake at previous meal, and is useful in planning meal sizes (Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011). Third, 7 day-food-diary reporting consecutive 21 BG measurements and meal compositions may prove to be a highly effective educational instrument to evaluate intake meal by meal as suggested in point two. Fourth, a mean of pre-meal BG sequence informs on lowest mean energy availability for the body. "Mean BG" is a metabolic characterization of an individual, energy meal pattern (fifth), which is standard in metabolic time and allows comparisons and classifications better than daily energy intake (Ciampolini & Sifone, 2011). Sixth, mean BG measures the blood function of providing energy to body tissues (Ciampolini & Sifone, 2011).

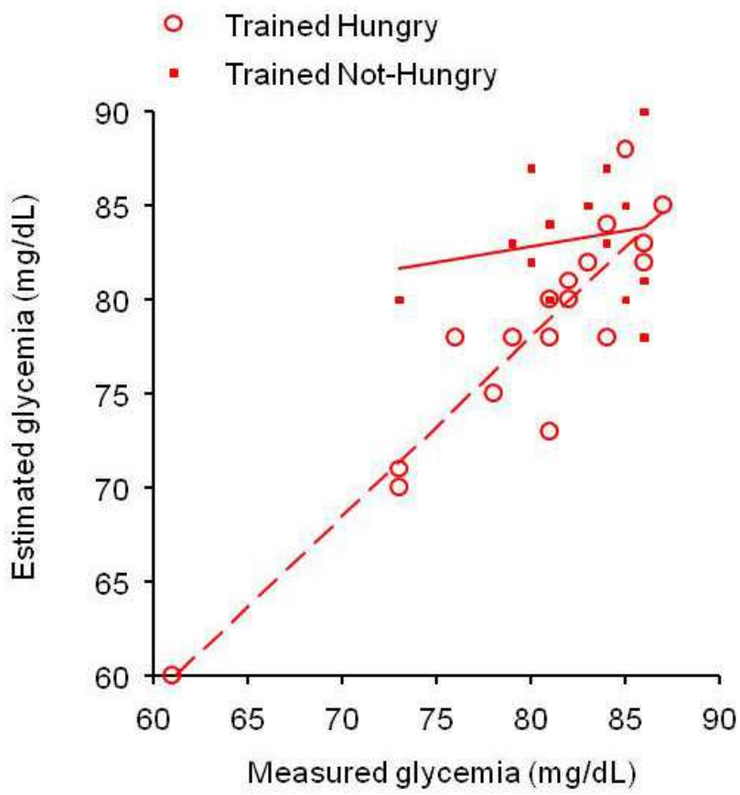


Fig. 2. Estimated *vs* measured blood glucose (BG) of trained subjects with BG below 87 mg/dL at the final session.
The highest BG measured in trained hungry subjects was 87 mg/dL. Below this value of measured BG, 18 subjects reported to be hungry (hollow red circles) and 14 subjects were not hungry (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: Ciampolini & Bianchi, 2006a).

Meal adaptation to "recognizing hunger" decreased mean BG, metabolic risks, insulin resistance and overweight in the trained group compared to control subjects (Ciampolini et al. 2010b). The global response in mean BG and the global improvement overlooks differences in single meal patterns, insulin sensitivity and health at recruitment and in response to training. If mean BG is maintained as a personal habit, the differences may explain huge risk differences that can be personally felt and corrected by "recognizing hunger".

1.2 Investigation aims

After suspension of food intake and initial identification of the first sensation of hunger, can a subject show a stable recognition of the same hunger sensation by coincidence between BG estimation and measurement? Can a subject maintain a meal rhythm based on recognition of the same subjective sensation (IH)? Can few subjects maintain the rhythm before any training? Can the trained rhythm decrease metabolic risk factors? Can prevent malnutrition and slightly depressed BG? Can decrease body weight in overweight people and in subjects with insulin resistance? The demonstration of these effects show that the achieved rhythm (mean BG) is homeostatic rather than being an artifact, i.e. maintains a BG that is constant and

both sufficient for activity and body weight maintenance, and effective in risk prevention. Informed people may approximate this *reference* model in eating as much as they can.

1.3 Subjects

A total of 181 subjects were recruited by the Paediatric Gastroenterology Unit of Florence University, a third level referring center, between 1995 and 2000 (Ciampolini et al. 2010). Subjects were gastroenterology patients between 18 and 60 years of age with functional bowel disorders, a self recovering disease. Subjects showed no morphological, physical or biochemical signs of organic disease. Subjects with impaired glucose tolerance (fasting plasma-glucose > 115 mg/dL (6.4 mmol/l)), as well as subjects suffering from non-insulin dependent diabetes mellitus (NIDDM), celiac, inflammatory bowel, liver, heart, brain and kidney diseases were excluded from recruitment. At end of investigation, 149 completed the protocol. 120 served for the metabolic study. All 149 were used for the body weight study. Informed consent was obtained from all participants. The local Hospital Ethics Committee approved the study in compliance with the Helsinki Declaration.

2. Metabolic study on 120 subjects

2.1 Design

All 120 subjects who completed the protocol were fully assessed at recruitment (before training), clinically only after the first 7 weeks of training, and completely at the end of the investigation (total investigation 5 months). In 31 control subjects, we investigated whether food intake is habitual, ie, maintaining the same meal pattern by "mean BG". Moreover, habits in BG maintenance may be personal, ie, sharply defined from most others. In all 120 subjects, we calculated mean confidence interval at recruitment (0.95%) for this purpose, and we stratified all 120 subjects in groups that contained subjects without significant differences in mean BG. Some subjects who had low mean BG at recruitment might fail any response to "recognizing hunger", because their meal pattern lowers mean BG to the point of imminent subjective insufficiency (see description of training) (Ciampolini et al. 2010a; 2010b; Ciampolini & Sifone, 2011). We decided to find the most significant cutoff point on the basis of individual response in mean BG (decrease), either significant or not. After finding the cutoff, we separately investigated (at recruitment and during "recognizing hunger" 5 months from recruitment, compared with controls) the association of subjects with low mean BG (LBG) and high mean BG (HBG) with insulin area under curve (AUC), and indices of insulin sensitivity and beta cell function (primary endpoints). Analyses were also performed on BG AUC, measurements of BG and insulin concentrations during oral glucose tolerance test (GTT), mean BG, and glycated hemoglobin (HbA1c) values (secondary endpoints). Data are presented post hoc division. Data without division have also been published and are not reported here (Ciampolini et al. 2010b).

2.2 Assessment of metabolic and health conditions

Additional analyses were performed on energy balance, cardiovascular status, well-being, and nutrition. i) Energy balance during the 5-month investigation interval was assessed through measurement of arm and leg skin-fold thickness changes, by measurements of body weight and body mass index (BMI) and by assessment of reported energy and vegetable

intake (Ciampolini et al. 1987; Ciampolini et al. 1990; Ciampolini & Bianchi, 2006a; Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011) ii) Cardiovascular status was assessed by systolic and diastolic blood pressures, plasma LDL cholesterol/HDL cholesterol ratio, triglycerides, and HDL cholesterol. iii) Structured interviews ascertained the number of days in which each of five functional symptoms (diarrhea, vomiting, headache, epigastric or abdominal pain) occurred during the previous three months (Ciampolini et al. 1987; Ciampolini et al. 1990). The hours of daily physical activity and time spent in bed reported in the seven-day diary were also assessed. iv) Nutrition was assessed by monitoring blood hemoglobin (Hb), mean cellular volume (MCV), transferrin saturation, plasma ferritin, zinc, folates, and vitamin B12 (Ciampolini et al. 1990).

2.3 Training to "recognizing hunger"

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. On the first day, subjects suspended food intake until arousal of a sensation of hunger, generally epigastric hunger (Ciampolini & Bianchi, 2006a). Meal consumption delayed two hours in average, 0 - 48 hours in range. At first arousal subjects memorized the sensation, measured BG by a portable instrument (See, please later) and consumed a meal. 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 (Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011). After showing association with constant BG, we named the three sensations of epigastric hunger, 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) (Ciampolini et al. 1987; Ciampolini et al. 1990; Ciampolini & Bianchi, 2006a; Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011; Ciampolini et al. 2001; Ciampolini, 2006b). Thus, subjects chose BG the first day on hunger sensations, in subsequent days learned the food amount per meal, and confirmed the chosen sensation as reference for intake by showing the same BG attainment before each meal. Both control (N = 31) and trained (N = 89) subjects had the same information on food energy contents, on recommended vegetable intake and physical activity amount per day.

2.4 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 being feverish, or under psychic stress because BG in these circumstances is higher than 1 hour after cessation of the transient metabolic condition (Ciampolini & Bianchi, 2006a). 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 pre-prandial sensation of epigastric hunger (Ciampolini et al. 1987; Ciampolini et al. 1990; Ciampolini et al. 2001; Ciampolini & Bianchi, 2006a; Ciampolini, 2006b; Ciampolini & Sifone, 2011). 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 labelled water in infants (Ciampolini, 2006b); glycated hemoglobin (HbA1c); methods for anthropometric measurements, structured interviews, and relevant clinical blood tests.

2.5 Preliminary findings and subgrouping

2.5.1 Stratification of 120 subjects by significant differences in mean pre-prandial BG

At recruitment, mean BG was distributed from 64.5 to 109.9 mg/dL in all 120 subjects, but the mean confidence interval (95%) of diary measurements around mean BG was ± 3.84 mg/dL. In Figure 3, all 120 subjects were stratified in ten groups by increasing mean BG at recruitment. Each of ten stratifications included subjects who showed no difference in mean for BG ($P > 0.05$), but excluded subjects who had significant differences (Armitage & Berry, 1994).

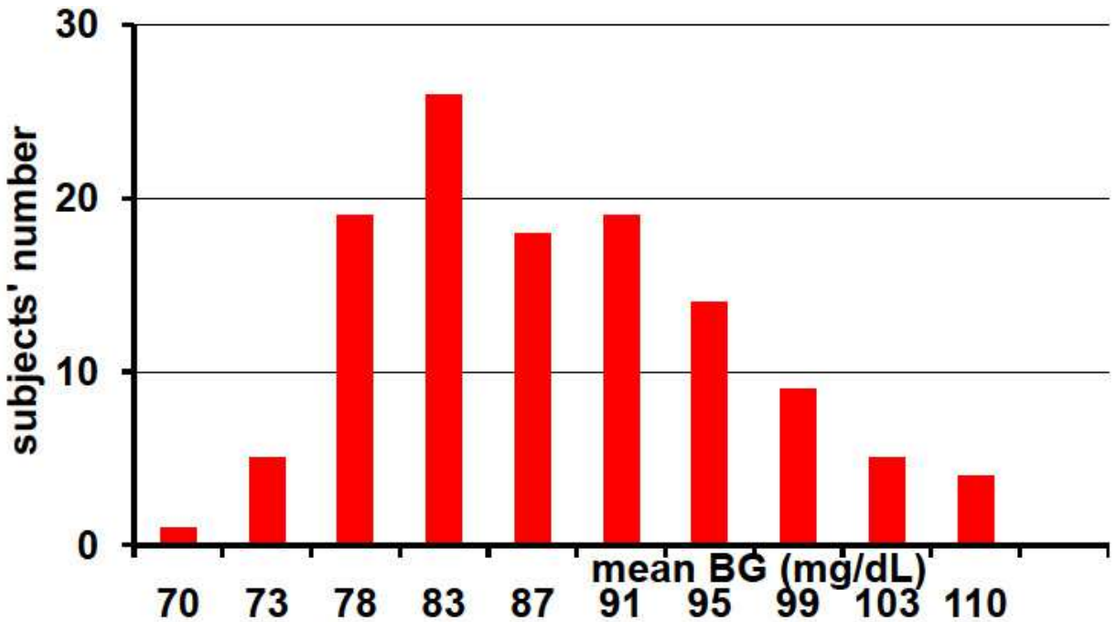


Fig. 3. Increasing sequence of mean blood glucose (mean BG) of all 120 trained and control subjects divided in 10 strata (columns) by significance of differences in mean BG at recruitment.

Strata consist of subjects with no significant difference in mean BG inside the stratum. Moreover each stratum excludes subsequent subjects whose mean BG is significantly higher than that of the first subject in the stratum. Column height shows the first component. Mean blood glucose reported in sequentially increasing order at recruitment, not in linear correlation with segment length on the x-axis scale. (By kind permission of the Authors: Ciampolini & Sifone, 2011).

2.5.2 Stability of mean BG in 31 control subjects

31 control subjects maintained a stable mean BG after 5 months (from 85.2 ± 8.1 mg/dL to 85.3 ± 7.6 mg/dL). The absolute pre/post change (increase or decrease) was 6.0 ± 4.6 mg/dL with a confidence interval (95%) from 3.1 mg/dL to 8.9 mg/dL.

2.5.3 LBG and HBG subgroups by response to "recognizing hunger"

Figure 4 shows the increasing mean BG sequence in 89 trained subjects and their response to "recognizing hunger" training. Significant decrease of mean BG by the end of the investigation occurred mainly in subjects with high mean BG at recruitment, whereas mean BG remained relatively constant in subjects with low BG at recruitment. A cutoff value (demarcation point) of mean BG that most significantly divided these two subgroups was identified, being 81.8 mg/dL (Figure 4: mean BG changes: post-minus pre-values as a function of the BG means at recruitment). 34 subjects below this "cutoff" (demarcation point) formed the low BG (LBG) subgroup. 55 subjects over this cutoff formed the high mean BG subgroup (HBG). Similarly, the BG value of 81.8 mg/dL was used to divide control subjects into LBG and HBG control subgroups (Tables 1 and 2).

2.6 Results from subgroups and discussion

2.6.1 Clinical events

About one third of subjects already maintained a mean LBG by free personal choice at recruitment. Others, motivated by bowel disorders, considered compliance as difficult before training and easy after training. Yet, the easy maintenance and the rapid recovery allowed sustained compliance. The functional disorder was significantly associated with high mean BG (and insulin resistance etc.) in HBG subjects, and possibly with high standard deviation of BG in LBG subjects (Table 2). In infants we suggested that positive balance of energy stimulates a diarrheic feedback (Ciampolini et al. 1990; Ciampolini et al. 1996). In the trained HBG group (Table 3), the decreases in days with abdominal pain or stomach-ache, were significant and significantly larger than in the control HBG group. In a national assistance design of risk prevention, recurrences of bowel disorder are sufficiently diffuse and sufficiently disturbing to motivate balance correction (training "recognizing hunger") and to improve insulin sensitivity in large part of population.

2.6.2 Stressful states

A large number of evidence shows an association between the emotional state of central nervous system and high levels of serotonin, cortisol, cortisol releasing factor and glucose in blood and/or mucosa (De Giorgio & Camilleri, 2004; Gershon, 1999; Spiller, 2008; Bischoff et al. 2009; van den Wijngaard et al. 2010; Wang et al. 2003; Lal et al. 2001; Ohman & Simrén, 2010; Spiller, 2008). These factors activate mast cells (Sand et al. 2009) and disrupt motility, secretion and absorption in mucosa (Dinan et al. 2006; Rana, 2009).

Persistence of these biological, infective stimuli and/or psychophysical stresses modify activity of monocytes, macrophages and mast cells, and together alter the neuro-endocrine system, and increase intestinal permeability. Bacterial biofilms may develop inside the alimentary canal and produce endotoxins that invade blood and all tissues (Ciampolini et al.

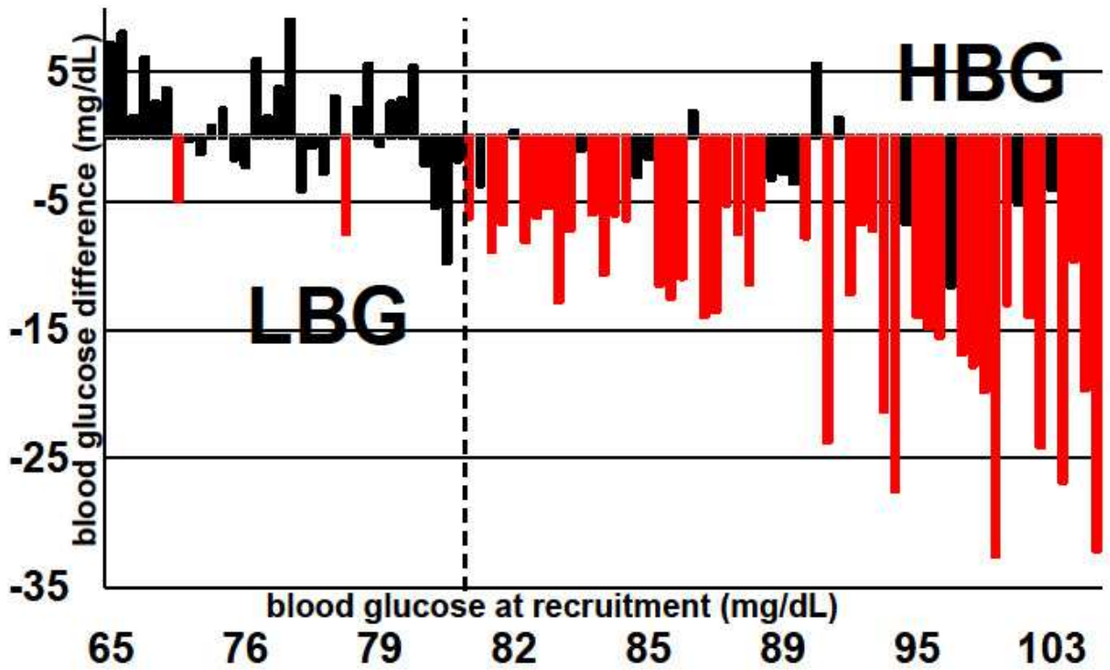


Fig. 4. Difference after training versus value in mean blood glucose for each trained subject at recruitment.

Column height shows 5-month post less pre mean blood glucose difference from 7d-diary in each trained subject. Significant decreases in red and not significant changes in black. Mean blood glucose reported in sequentially increasing order at recruitment, not in linear correlation with segment length on the x-axis scale. The dashed division indicates the most significant division between subjects who showed no mean blood glucose decrease after training (LBG group, n = 34 subjects) and those who showed significant decrease of mean blood glucose (HBG group, n = 55 subjects; $\chi 2$ analysis: P = 0.00001). This threshold blood glucose (demarcation point) is 81.8 mg/dl (4.5 mmol.l) at recruitment. (By kind permission of the Authors Ciampolini & Sifone, 2011).

1996). Locally, an inflammatory process develops in mucosa and may persist for months and years. (Tornblom et al. 2002; Ohman, L. & Simrén, 2010; Spiller, 2008). Locally, the process is minimal, because of intestinal tolerance (Brandtzaeg et al. 1989). Inside the intestine, a minority (10% - 20%) of bacterial species are immunogenic although being incapable of promoting a general illness such as Salmonella species do (van der Waaij et al. 1996). Immunogenic bacteria induce a huge biological activity of human immune system and a deep functional alteration (Reaven, 2006; Festa et al. 2000). Body tissues develop a pro-inflammatory state (subclinical inflammation, a synonym) that is sterile, ineffective and dangerous for body tissues in the intestine, vascular bed and elsewhere (Reaven, 2006; Festa et al. 2000). The invasion of body tissues by bacterial products and endotoxins sustains subclinical inflammation and causes the slow progression of many chronic diseases.

The start of the subclinical inflammatory process is controversial. Stress is associated with a condition of high BG and insulin resistance. This condition is causally associated with a "pro-inflammatory state" or "subclinical inflammation". General acceptance of this causal association took unfortunately 80 years (Kylin, 1923; Randle et al. 1963; Festa et al. 2000; Reaven, 2006). Stressed people may eat as usually, and even more, disregarding any hunger

or signs of low BG (Robbins & Fray, 1980; Flaa et al. 2008). This meal pattern can maintain intestinal disorders for years (Zwaigenbaum et al.1999), and may contribute to current epidemic of insulin resistance, obesity (Flaa et al. 2008), subclinical inflammation and vascular diseases (Reaven, 2006; Festa et al. 2000; Kahna et al. 2005; Cefalu, 2005; Moller & Flier, 1991; Mather & Verma, 2005; Weiss et al. 2004). On the contrary, "recognizing hunger" prescribes transient suspension of intake during stress and in the subsequent hours until BG lowering (Table 7). Implementation of "recognizing hunger" definitively stopped intestinal disorders in adults (Table 3) and relapses in children (Ciampolini et al. 1987; Ciampolini et al. 1990; Ciampolini et al. 1991; Ciampolini et al. 1994; Ciampolini et al. 1996; Ciampolini et al. 2000; Ciampolini & Sifone, 2011).

2.6.3 Subjective and objective assessments

The training was subjective. Subjects learned to recognize IH in the first day and adapted intake to the arousal of this target sensation three times a day. The BG association checked the consistency of the recognition ("recognizing hunger").

	Low BG group				High BG group			
	Control		Trained		Control		Trained	
	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.
Number of subjects and Gender	8 F + 4 M		21 F +13 M		6 F + 13 M		25 F + 30 M	
Schooling (years)[1]	12.0±3.2		12.9±2.7		9.8±4.4		11.4±3.7	
Age (years)[1]	28.3±8.2		32.2±8.5		30.5±9.2		32.8±11.4	
BMI	21.8±3.4	21.9±3.1	22.6±3.3	22.0±2.7^{**,b}	22.4±5.1	23.0±4.1	23.2±4.0	22.1±3.4^{**,a***,b}
Weight (Kg)	57.5±8.4	57.7±8.9	62.4±11.1	60.8±9.9^{*,b}	60.9±12.2	62.9±8.4	65.2±13.4	62.7±12.1^{**,a***,b}
Arm skin-fold thickness (mm)	15.6±9.8	15.7±9.5	15.4±8.4	13.3±6.4^{*,b}	14.9±10.2	13.9±7.2	16.4±7.9	12.8±6.0^{*,a**,b}
Leg skin-fold thickness (mm)	21.7±13.5	21.7±13.4	20.1±10.8	17.3±8.0^{**,b}	20.0±11.8	18.6±9.4	22.5±11.4	17.5±8.8^{*,a,**,b}

Values are expressed as means ± SD. [1], values at the beginning of the study. *Asterisks* indicate a significant difference (Student's *t*-test: *, P < 0.05; **, P < 0.01; ***, P < 0.001) on pre/post difference *vs.* respective control group (*a*), or *vs.* value of the same group at recruitment (*b*).

Table 1. Group composition and effects of training on anthropometry in low and high BG subjects.

.	Low BG group				High BG group			
	Control		Trained		Control		Trained	
	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.	Recruit-ment	After 5 mo.
Mean pre-meal BG (mg/dL)	76.9 ± 3.4	79.1±3.5	76.6±3.7	77.2±4.2	90.4±5.3	89.2±6.9	91.6±7.7***,*c*	81.0±7.7 ***,*a* ***,b
BG diary SD (mg/dL) [1]	7.6±2.3	8.7±1.7**,*b*	6.8±3.0	5.4±2.3 *,*a* **,*b*	9.0±3.3	9.3±3.9	9.4±4.8**,*c*	6.6±2.6**,*a* ***,b
Glycated Hb (%)	4.38±0.29	4.53±0.35	4.50±0.30	4.43±0.31	4.65±0.38	4.83±0.39	4.81±0.44***, *c*	4.56±0.47 ***,*a* ***,b
Insulin AUC[2] (mU $L^{-1}3h^{-1}$)	192±106	243±133	180±98	183±83*,*a*	222±81	215±98	244±138*,*c*	164±92**,*a* ***,b
Insulin peak (mU L^{-1})	66±30	83±41	62±44	58±30	75±33	68±36	79±46**,*c*	54±29*,*a* ***,b
Insulin sens. (index)[3]	14.6±7.2	11.8±5.8	15.9±8.3	15.7±9.0	6,0±2.2	6,8 ± 3,9	5.9±3.3***,*c*	9.8±5.6**,*a* ***,b
Insulingenic c index [4]	0.9 ±0.6	0.8±0.6	0.9±0.9	1.0±0.7	1.1±1.2	0.7±0.7	1.0±0.7	1.4±1.1**a* *,b
BG AUC (mg/dL)	547±117	542±126	548±73	537±81	627±101	598±107	639±98***,*c*	567±91***, *b*
BG peak (mg/dL)	124±25	124±30	119±22	122±24	136±22	128±27	145±27***,*c*	128±27***, *b*
Energy intake (kcal/d)	1803±567	1565±677	1568±612	1303±590***, *b*	1887±599	1703±557	1872±655*,*c*	1251±470 ***,*a* ***,b
Meals per day[5]	3.7±0.7	3.8±0.6	3.8±0.6	3.5±0.5**,*b*	4.0±0.7	3.9±0.7	3.9±0.7	3.7±0.7***, *b*
Vegetable intake (g/d)	272±265	292±223	388±257	492±217*,*b*	127±128	166±218	287±223*,*c*	392±251**, *b*
Fruit intake (g/d)	183±177	188±205	233±152	334±315	183±133	147±113	214±150	290±219**,*a* *,b

[1] diary SD refers to the mean of the mean BG standard deviations of 21 measurements reported by each of 7d diary.
[2] AUC = area under GTT curve.
[3] Whole body insulin sensitivity index (Matsuda & DeFronzo, 1999).
[4] Insulinogenic index of beta cell function (Wiesli et al. 2004).
[5] Meal was an event of higher intake than 20 kcal.

Values are expressed as mean ± SD. Peak values include different observations from those at 30′ during GTT. *Asterisks* indicate a significant difference (Student's *t*-test: *, P < 0.05; **, P < 0.01; ***, P < 0.001) on pre/post difference *vs.* respective control group (*a*), or *vs.* the value of the same group at recruitment (*b*), or *vs.* the value of LBG trained group at recruitment (*c*).

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

We assume that a week sequence of BG measurements before meals shows the least energy availability to body cells in that week, and the mean value at this metabolic moment represents the standardized parameter that we needed in the evaluation of habitual energy balance (meal pattern) in relation to its main function, provision of energy to body. Mean BG was maintained as a habit in control subjects, i.e. for a longer period than a week, and was personal, at different level from one person to another. Before initial abstinence from food (before training), HBG subjects habitually forestalled the arousal of the physiological regulation mechanism and maintained positive energy balance. On the basis of the high standard deviation of BG (Table 2 and 7), the meal pattern of untrained LBG subjects was irregular from a meal to another in comparison with during "recognizing hunger", despite of null balance, of low mean BG and weight stability in a long period (see, please, later). We cannot conclude that LBG coincided with "recognizing hunger" (See, please, later).

2.6.4 Unremitting adjustment to energy expenditure

The food diary with pre-prandial BG measurements served moreover as an educational instrument. We trained (and checked) "recognizing hunger" in adjusting intake to sensations meal by meal by the reported diary. Changes in skinfold thickness, i.e. five-month energy balance, showed reliability of the reported "recognizing hunger" (Tables 1 and 7). Within this view, dieting represents a rough attempt to achieve an ideal (?) weight without understanding and implementing the necessary meal by meal adjustments to expenditure.

2.6.5 Sufficient intake by "recognizing hunger"

As regards normal-weight subjects, trained HBG but not LBG subjects showed a cumulative balance that was negative in the 5 months, and the longitudinal difference was significant in comparison with control subjects (Table 7). The significant decrease of glycated hemoglobin (Table 2) and of body weight, BMI and arm and leg skin-fold thickness in HBG group and the stability of LBG group (Table 7), confirmed the persistence of reliability throughout 5 months of this investigation, and also the meal adjustments by "recognizing hunger" to expenditure. The maintenance of previous physical activities in all trained subjects and the improvement in nutrition parameters in HBG subgroup (Table 3) demonstrate that meals taken by trained subjects were sufficient to meet energy needs. This confirms earlier controlled, randomised studies in children with chronic non-specific diarrhea, in which daily activity was preserved and body weight increased normally after seven months, 4 years and 12 years of complying with a pediatric adaptation of the present training (Ciampolini et al. 1990).

We adapted "recognizing hunger" to infants, and the initial request of children substituted initial hunger (Initial Request Meal Pattern, IRMP) (Ciampolini et al. 1990). In 73 infants (Ciampolini, 2006b), the cutoff at 81.2 mg/dL divided subjects with low mean BG from those with high mean BG at recruitment by the highest significance. 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 chapter and to the cutoff found in prevention of non-insulin dependent diabetes in Israeli recruits (Tirosh et al. 2005).

In the same preliminary work (Ciampolini, 2006b), 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 (Ciampolini, 2006b). IRMP decreases mean BG, RMR and TDE in infants. We interpreted 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, "recognizing hunger" decreased mean BG, RMR and TDE, meal by meal positive balance in blood, insulin resistance, intestinal disorders, and vascular risks (subclinical inflammation). Table 4 has not been published, except for 6 groups. There are findings on mean BG from 9 different groups.

		Control		Trained	
		Recruitment	After 5 mo.	Recruitment	After 5 mo.
Well being trial	Vomiting (days with vom./90 days)	0.1±0.3	0.1±0.2	0.2±0.9	0.1±0.5
	Headache (days with pain/90 days)	12.3±27.8	8.8±20.9	6.2±13.4	1.9±4.9**,b
	Diarrhoea (days with diarrhoea/90 days)	2.0±0.6	0.6±1.4	5.6±15.7	0.6±2.8 **,b
	Abdominal pain (days with pain/90 days)	5.8±20.5	5.9±20.6	7.6±13.6	1.0±2.0 ***,a ***,b
	Stomach ache (days with pain/90 days)	7.3±11.0	2.2±4.6	7.5±11.4	0.5±1.9 ***,a ***,b
	Outdoor and gym hours (hours/d)	4.3±3.4	3.8±3.4	3.5±2.9	4.2±2.9 *,a
	Bedtime (hours/d)	8.4±0.7	8.3±0.9	7.91.0	7.7±1.1
Cardio vascular trial	Systolic blood pressure (mm Hg)	114.7±15.0	112.3±12.2	114.1±16.4	106.3±15.2 **,b
	Diastolic blood pressure (mm Hg)	64.7±12.1	69.2±11.0	70.4±12.6	65.5±11.5 **,a *,b
	Triglycerides (mg/dL)	87.7±65	68.0±36	73.8±30.7	71.3±33.2
	HDL cholesterol (mg/dL)	52.9±14.3	44.9±14.9	45.4±14.6	52.0±13.9 **,a **,b
	LDL cholest./HDL cholest. ratio	2.1±0.9	2.7±1.5	2.9±1.5	2.3±1.2 **,a **,b
Nutrition trial	Hemoglobin (g/dL)	13.3±0.6	13.5±0.9	13.3±1.5	13.4±1.4
	MCV (micr3)	86.9±5.5	85.6±3.7	87.4±6.5	87.2±6.4
	Transferrin Sat. (%)	45.9±17.8	43.8±15.0	37.1±16.9	40.3±17.0
	Ferritin (ng/ml)	42.7±41.8	42.4±17.3	63.1±58.5	68.4±56.6
	Zn (micrgr/dL)	86.0±29.2	80.1±14.5	77.8±24.4	81.9±20.7
	Folates ng/ml	7.9±4.4	8.3±4.3	9.6±4.6	11.3±4.9
	B12 (pg/ml)	567±465	438±149	544±262	590±264

*, suppressed for Bonferroni correction. **, ***, [a] and [b] symbols as in Table 2.

Table 3. Effects of training on well-being, cardiovascular, and nutrition parameters in HBG groups.

2.6.6 Diabetes prevention

It is interesting that insulin production decreases with increasing non-insulin dependent diabetes (NIDD) duration and HbA1c height (Wiesli et al. 2004). In this investigation, the HBG control subgroup decreased insulinogenic index of beta cell function whereas the HBG trained subgroup increased it (Table 2). The difference between control and trained subgroups was significant, this implies higher insulin production, preservation of beta cell function and the possibility of an innovative therapy designed to preserve or even improve functional beta-cell mass by "recognizing hunger" (Wiesli et al. 2004). 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 non insulin-dependent diabetes (NIDD) in men compared to those whose fasting plasma glucose was < 81 mg/dL (4.5 mmol/l) (Tirosh et al. (2005). Assessment and classification of meal habits allows correction toward metabolic risk decrease as in Framingham studies (Singer et al. 1992).

Training [1]	Before	After
34 adults (BMI from 17 to 40)[2]	76.6 ± 3.7 2	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 normalweight adults, ctrl	77.3 ± 3.9	No training
26 normalweight 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 [23]	91.7 ± 7.8	78.5 ± 6.8
41 HBG infants [4]	92,3 ± 7,7	74,7 ± 5,1

[1] Trained subjects show mean BG both before and after training. No training refers to subjects kept as control (ctrl).
[2] Mean ± SD of mean diary of 21 pre-prandial BG in a week in mg/dL, (present report, subchapter 2).
[3] 41 of 55 adults of mixed body mass index (BMI) and mean BG > 81.8 mg/dL at recruitment who significantly decreased mean BG after training "recognizing hunger" (present report, subchapter 2).
[4] 41 of 55 HBG infants of 73 recruited for 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 4. Occurrence of low mean blood glucose (LBG) either by free, spontaneous choice (Before) or after training (After) "recognizing hunger" in 9 different groups

2.6.7 Diabetes treatment

In this report, "recognizing hunger" either prevented or cured insulin resistance and NIDD in young, clinically healthy, adults with "normal" BG. A condition of insulin sensitivity suppresses subclinical inflammation (pro-inflammatory state) and the associated functional disorders and evolving vascular diseases (Reaven, 2006; Festa et al. 2000; Kahna et al. 2005; Cefalu, 2005; Moller & Flier, 1991; Mather & Verma, 2005; Weiss et al. 2004). "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" (Ciampolini & Bianchi, 2006a). The low error validates "recognizing hunger", and prevents regaining body weight (Table 7),(Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011). 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.

2.6.8 Prevention of vascular diseases

In tables 2 and 3, the untrained meal pattern of HBG subjects was positively associated with energy intake, mean BG, insulin resistance, glycated hemoglobin, diastolic blood pressure, high LDL to HDL cholesterol ratio, and low HDL cholesterol. Briefly, these associations form the 'metabolic syndrome, which is strongly associated with development of bacteria in small intestine (Ciampolini et al. 1996), high absorption of microbial antigens (Brandtzaeg et al. 1989; Kinugasa et al. 2000; Perez et al. 2007), subclinical inflammation and vascular diseases (Reaven, 2006; Festa et al. 2000; Kahna et al. 2005; Cefalu, 2005; Moller & Flier, 1991; Mather & Verma, 2005; Weiss et al. 2004). Subclinical inflammation develops in blood and on endothelia, and may become clinically relevant in every tissue for local presence of additional inflammatory factors. Bronchitis becomes respiratory distress, and ankle trauma becomes local arthritis. "Recognizing hunger" was associated with lowering the habitual BG and disappearing of metabolic syndrome and risks of vascular disease. "Recognizing hunger" decreased body weight in normal weight adults who were insulin resistant, and in overweight adults (BMI > 25)."Recognizing hunger" decreased insulin resistance index, HbA1c, and increased the insulinogenic index of beta cell function in 55 HBG of 89 trained subjects as compared to control subjects. In future investigations on the risks due to high blood pressure, "recognizing hunger" and achievement of insulin sensitivity may prove far better than drug control of blood pressure and thrombotic tendency.

2.6.9 "Recognizing hunger" fading and overlapping over HBG

Mean BG had little absolute change (13.2% ± 10.1% of the range at recruitment in mean BG in the 120 investigated subjects: 64.5 mg/dL to 109.9 mg/dL) in control subjects over 5 months. The division of all 120 subjects in ten strata at recruitment was a classification of associated meal pattern. Subjects chose "recognizing hunger" at the lowest level of BG availability during the day. No surprise if "recognizing hunger" largely coincides with LBG meal patterns. The point of mean inversion was at 81.8 mg/dL. However, 27 out of 89 subjects further persisted at HBG level at final investigation although 15 out of 27 were within LBG limits after seven weeks training. 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 all 27 other subjects. They reported pre-prandial IH and were insulin sensitive (Table 5). IH developed in these heavy outdoor workers at higher levels than 81.8 mg/dL for high expenditure (Table 5). The division between compliance and no compliance with "recognizing hunger" is statistically strong at

81.8 mg/dL, but single subjects who actually comply with "recognizing hunger" may show higher mean BG than 81.8 mg/dL, an overlapping over HBG.

	6 HBG [1]	21 HBG [2]
Mean Blood glucose (mg/dL)	86.4 ± 4.0	87.1 ± 5.3
Final insulin AUC (mU $L^{-1}3h^{-1}$)	124 ± 26	207± 99 **
Final blood glucose AUC (mg $dL^{-1}3h^{-1}$)	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

*, **, *** symbols as in Table 2.

[1] 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.

[2] 21 HBG subjects included 15 that were LBG after seven weeks training (clinical assessment) and six who had higher mean BG than 100 mg/dL at recruitment.

Table 5. Effects of heavy outdoor work[1] in 27 trained subjects who remained with high BG at investigation end.

3. Body weight study on 149 subjects

3.1 Effects of "recognizing hunger"

The study on 120 adults included 30 overweight (OW) subjects. This number was not sufficient to draw separate conclusions on responses of LBG and HBG OW subjects to "recognizing hunger". We had however treated and investigated also OW subjects who had not performed blood examinations. We thus could add 29 OW subjects to the 120 subjects that we reported up to now (Table 6). We trained these OW subjects and collected 7-d-food intake diaries like in previous investigation. We randomized 90 NW subjects separately from 59 who were OW to the control and the trained groups. We assigned both control and trained, NW and OW subjects to LBG and HBG subgroups on the basis of diary mean BG. The cutoff was 81.8 mg/dL (Figure 4) (Ciampolini et al. 2010a; Ciampolini & Sifone, 2011).

"Recognizing hunger" (IHMP) led to loss of weight in subjects who are either OW or who are of NW with HBG (Table 7). In NW LBG subjects, weight was maintained (Ciampolini et al. 2010a). The division between normal-weight and overweight people is based on a significant increase of vascular diseases over the limit of 25 for BMI. About 20% of people below 25 BMI is at increased risk for vascular diseases (Colditz, 2004; Weiss et al. 2004). The present report is in agreement with this statement: forty of 55 HBG subjects were NW and insulin-resistant (Table 2 and 7). Maintenance of high BG and of the associated insulin resistance provokes the increased risk, although subjects may have a small fat increase, insufficient to overcome the limit of 25 BMI, and insufficient to be classified as overweight (Table 7). Insulin resistance is a sort of fattening that remains below 25 BMI in lean subjects, and is thus un-apparent even by an esthetical evaluation. People with thin bones and thin muscles are at high risk of intentional fat accumulation (and associated insulin resistance). They may increase subcutaneous fat to improve their figure, and become insulin-resistant by remaining NW or even thin!

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.
Number of subjects and gender	5 F + 4 M		16 F +10 M		3 F + 12 M		19 F + 21 M	
Schooling[1]	11.8±3.5		13.3±2.9		10.3±4.7		11.2±3.8	
Age[1]	27.9±8.2		31.0±8.9		29.3±2.5		29.7±8.9	
Subjects showing BG decrease[2]	0/9 (0.0%)		3/26 (11.5%)		6/15 (40.0%)		33/40 (82.5%)**,a	
BG group mean pre-meal[3]	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
Subjects < 81.8 mg/dL[4]	9	7	26	22	0	1	0	25***,a
Vegetable intake[5]	228±217	238±226	403±273	504±235	133±151	142±158	247±240	368±246 *,a**,b
Fruit intake[5]	150±122	146±75	246±162	376±346	161±91	143±123	201±157	291±218 *,a*,b
OVER-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.
Number of subjects and gender	6 F + 2 M		9 F +3 M		7 F + 6 M		14 F + 12 M	
Schooling[1]	11.8±3.0		12.3±2.6		10.6±4.0		11.9±3.3	
Age[1]	32.8 ±12.7		35.0±6.7		34.3±15,4		37.5±15.3	
Subjects showing BG decrease[2]	1/8 (12.5%)		2/12 (16.7%)		2/13 (15.4%)		22/26 (84.6%)***,a	
BG group mean pre-meal[3]	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
Subjects < 81.8 mg/dL[4]	8	5	12	10*,a	0	0	0	19***,a
Vegetable intake[5]	194±95	373±232	333±169	514±197	278±225	460±284 *,b	247±160	420±224 ***,b
Fruit intake[5]	138±121	182±219	214±138	223±124	226±168	167±121	225±116	286±191

Values are expressed as means ± SD. [1], years at the beginning of the study. [2],Number of subjects who significantly decreased mean pre-meal diary BG . [3],Mean pre-meal of diary blood glucose, mg/dL, LBG = lower than 81.8 mg/dL. HBG = higher than 81.8 mg/dL [4], Number of subjects who fell into the LBG at end of the study. [5], grams/d. *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 6. Normal- and over-weight groups divided by low and high mean pre-meal diary blood glucose (BG). Composition and compliance at baseline and at investigation end.

3.2 Possible mechanisms and explanations

We suggested above (background) that IH may begin an important afferent arm of a physiological regulation mechanism that provides meal-by-meal feedback on energy need thus optimizing energy intake (Ciampolini et al. 1996). Subjects who are overweight and those who are normal-weight but have pre-meal HBG forestalled this homeostatic mechanism. Restoring the homeostatic mechanism would explain our finding that

"recognizing hunger" (IHMP) leads to loss of weight in OW and NW HBG subjects but not in NW LBG subjects (Ciampolini et al. 2010a).

3.3 Training period and 7-day diaries

Implementation of "recognizing hunger" was associated with significant decrease of mean weekly BG as compared to control subjects. Glycated haemoglobin reflects the average BG over a 4 month period (Singer et al. 1992) and the lowered glycated haemoglobin (table 2) and significant weight loss observed in this study are unlikely to have occurred in the final week. These data suggest that awareness of IH indeed preceded final diary BG measurements, and was not significantly affected by it.

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
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
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

[1] Kcal/d. [2], mg/dL; diary SD refers to BG SD of 21 measurements reported by each of 7d diary. [3] body weight kg/square height meters. [4] Kg [5] mm. *Asterisks* indicate significant differences as in Table 1.

Table 7. Effects of training (IHMP) on diary reports and anthropometry in normal- and over-weight groups divided by low and high mean pre-meal BG.

3.4 Clinical and research implications: Advantages over conventional dieting

3.4.1 Restraint approach

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. Control OW LBG subjects showed a mean pre-meal 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 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.

Weight cycling is a well-described phenomenon (Colditz, 2004). In the first phase of the cycle intake is conditioned or non-homeostatic. This leads to positive energy balance and weight increase. In the second phase OW subjects restrain their eating to lose weight. Most likely, the OW LBG subgroup was in this second phase at baseline. In the post-absorptive state, OW subjects have been shown to mobilise three times greater amounts of energy from reserve tissues to blood compared to NW subjects (Corcoran et al. 2007). By attending to preprandial arousal of IH, trained OW LBG subjects had to adjust meal energy intake downwards sufficiently to take into account the increased availability of energy owing to postabsorptive energy release, hence their lower energy intake (about 300 kcal per day) compared to trained LBG NW subjects (Table 7). During established application of "recognizing hunger", OW subjects reported that, provided meals were not delayed, their hunger was of no greater intensity nor more prolonged than NW subjects. Moreover, despite significantly higher body weight and lower energy intake than NW LBG subjects, trained OW LBG subjects showed the same mean preprandial BG as trained NW subjects (Table 6 and 7). These findings have at least three important clinical and research implications:

Trained OW subjects do not need to endure more prolonged or more intense hunger than trained NW subjects in order to lose weight.

The IHMP ("recognizing hunger") allows loss of weight without compromising energy availability for day-to-day energy need. The input of fatty acids from fat tissues to blood is limited in the overweight. Diets with lower mean content than 900 kcal a day may yield insufficient energy for body functions. That preprandial BG in the OW LBG group was the same as the NW LBG group indicates that in the OW LBG group a sufficiently high BG concentration was maintained for immediate energy needs. SD of diary BG in trained OW groups significantly decreased and regressed to that of NW groups further suggesting that under the IHMP ("recognizing hunger") OW groups adapted energy intake to metabolic need. In the absence of energy deprivation, less cycling of intake among trained OW groups would be expected.

An important subgroup exists (NW HBG) who appear NW by BMI criteria but who may nevertheless be at risk of weight related complications since they lose weight and decrease BG to a concentration comparable to the LBG group when trained to "recognizing hunger" (Tables 5 and 6).

3.4.2 Food composition approach (increased vegetables)

After 5 months, no significant difference was found in vegetable intake between control and trained subjects. At the end of the study controls did not attain significantly lower BG or body weight than the trained group although they had been encouraged to lose weight. This implies that high vegetable intake alone is insufficient in preventing conditioned meals and lowering high BG (Tables 6 and 7).

3.4.3 Advantages of immediate feedback

Subjects following the IHMP ("recognizing hunger") receive meal-by-meal subjective feedback from physiological signals (Ciampolini et al. 1996). These signals map closely to BG and allow subjects to eat in an unconditioned manner without self-imposed restraint or the necessity to seek any particular goal weight. The resulting improved energy balance leads to loss of weight. "Normal weight" is an artificial construct based on population statistics and may not apply to a given individual. Recommendations of goal weight may be unhelpful for some subjects to whom the goal may seem arbitrary and daunting especially if it is to be achieved by dietary restraint. The IHMP ("recognizing hunger") obviates the need for pursuit of a statistical norm and allows each individual to find his or her physiological norm.

This approach could thus prove useful in the clinical setting since it removes major obstacles to weight loss – the need for restraint, the need for dietary change, and the need to attain an arbitrary weight goal.

3.5 General interpretation

Even before any training, a consistent minority maintains a meal pattern that is similar to "recognizing hunger", and is similarly associated with improved insulin sensitivity (Table 2) and normal weight (Table 7) (Ciampolini et al. 2010; 2010b; Ciampolini & Sifone, 2011). Others may easily and reliably learn "recognizing hunger" (IHMP) to improve insulin sensitivity and lose weight, and can easily maintain this meal pattern below the age of 60 years. The IHMP ("recognizing hunger") could therefore be an important tool in the clinical management of overweight and obese patients and could have implications for health policy in the prevention of a wide range of metabolic and vascular disorders.

4. Conclusions

People share sounds and figures with other people but not subjective sensations. Subjective sensations guide the intake, but nobody knows sensations reported from others. Present investigation validated initial hunger (IH) by BG, and created a rhythm of meals at the arousal of IH, which decreased vascular risks. A three-times- daily meal pattern ("recognizing hunger" or IHMP) was associated with low mean blood glucose (LBG) and sustained regression of overweight and of the fat excess that is associated with insulin resistance, metabolic syndrome, subclinical inflammation and vascular diseases. Post hoc division of NW and OW subjects into subgroups with mean pre-meal BG either lower or higher than 81.8 mg/dL suggests body weight maintenance in NW subgroup with low mean BG and decrease in those who were either OW or HBG NW. The method was more effective than restraint-type dieting in a 5 month trial. IH, validated by BG, may represent

the recovery of a vital afferent arm of the body's homeostatic energy regulation system allowing sustained self-regulation of energy intake.

Present findings suggest that the current epidemic of insulin resistance and overweight may have its origin in the non-cognizance of hunger – the physiological signals of energy insufficiency to body cells. Lack of a subjective limit in intake (a similar limit to arousal of initial hunger) explains current epidemic of insulin resistance and overweight, This may owe to forestalling such signals in early life and subsequent reinforcement of this behavior pattern. Training "recognizing hunger" rationalized the arousal of the subjective, validated limit in order to acquire and maintain energy homeostasis in blood, and decrease vascular risks. The achieved rhythm (mean BG) is homeostatic rather than being an artifact, i.e. maintains a BG that is constant and both sufficient for activity and body weight maintenance, and effective in the prevention and treatment of diabetes and obesity and a range of associated disorders and thus lessen the high economic burden of health services in industrialized societies.

5. Acknowledgments

The author wish to thank Laura Chiesi and Stefania Bini MD for dietary analyses, Riccardo Bianchi, David Lovell-Smith, Andrea Giommi (Statistics professor) and Stella Zagaria for technical support and insights, Stephen Buetow, Tim Kenealy, Chris Harshaw, Simon Thornton, Kent Berridge, James Gibbs, Charlotte Erlanson-Albertsson and Michael Hermanussen for helpful insights on earlier drafts of this paper. This research was supported by the Italian Ministry of University, Research, Science and Technology grants for the years 1998–2002 and ONLUS Nutrizione e Prevenzione, Firenze for years 2003–2008. The authors declare that they have no competing interests.

6. List of abbreviations

IHMP: Initial hunger meal pattern = "Recognizing Hunger"
AUC: area under curve at GTT
BMI: body mass index (body weight in kg/square height in m)
BG: blood glucose concentration (glycemia)
GTT: oral glucose tolerance test
HBG: high mean BG (> 81.8 mg/dL)
LBG: low mean BG (< 81.8 mg/dL)
NIDD: non-insulin dependent diabetes
Mean BG: mean of 21 pre-prandial blood glucose measurements reported by 7 day diary
Diary-BG standard deviation: Mean pre-meal blood glucose standard deviation 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.

7. References

Armitage, P. & Berry, G. (1994). Statistical Methods in Medical Research, Blackwell, Oxford, UK, 3rd edition.

Brandtzaeg, P. et al. (1989). Immunobiology and immunopathology of human gut mucosa: humoral immunity and intreaepithelial lymphocytes. Gastroenterology, 97, 1562-1584.

Bischoff, S.C. et al. (2009). Role of serotonin in intestinal inflammation: knockout of serotonin reuptake transporter exacerbates 2,4,6-trinitrobenzene sulfonic acid colitis in mice. Am. J. Physiol. Gastrointest. Liver Physiol., 296, G685-G695.

Cefalu, W.T., (2005). Glycemic Control and Cardiovascular Disease — Should We Reassess Clinical Goals?. N. Engl. J. Med., 353, 2707-2709.

Ciampolini, M. et al. (1987). Internal stimuli controlled lower calorie intake: effects after eight months in toddler's diarrhoea. Ital. J. Gastroenterology, 19, 201–204.

Ciampolini, M. et al. (1990). Normal Energy intake range in children with chronic nonspecific diarrhea: association of relapses with the higher level. J. Pediatric Gastroenterology and Nutrition, 11, 342–350.

Ciampolini, M. et al. (1991). Decrease in serum IgE associated with limited restriction in energy intake to treat toddler's diarrhea. Physiology and Behavior, 49, 155–160.

Ciampolini, M. et al. (1994). Same growth and different energy intake over four years in children suffering from chronic non-specific diarrhea. International J. Obesity, 18, 17–23.

Ciampolini, M. et al. (1996). Microflora persistence on duodeno-jejunal flat or normal mucosa in time after a meal in children. Physiology and Behavior, 60, 1551-1556.

Ciampolini, M. et al. (2000). Attention to metabolic hunger and its effects on Helicobacter pylori infection. Physiology and Behavior, 70, 287–296.

Ciampolini, M. et al. (2001). Attention to metabolic hunger for a steadier (SD decrease to 60%), slightly lower glycemia (10%), and overweight decrease (Abstract). Appetite, 37, 123-172.

Ciampolini, M. & Bianchi, R. (2006a). Training to estimate blood glucose and to form associations with initial hunger. Nutrition and Metabolism, 3, 42

Ciampolini, M., (2006b). Infants do request food at the hunger blood glucose level, but adults don't any more (Abstract). Appetite, 46, 345.

Ciampolini, M. et al. (2010a). Sustained self-regulation of energy intake. Loss of weight in overweight subjects. Maintenance of weight in normal-weight subjects. Nutrition and Metabolism, 7, 4

Ciampolini, M. et al. (2010b). Sustained Self-Regulation of Energy Intake: Initial Hunger Improves Insulin Sensitivity. J. Nutrition and Metabolism, Article ID 286952.

Ciampolini, M. & Sifone, M. (2011). Differences in maintenance of mean blood glucose (BG) and their association with response to "Recognizing Hunger". International J. Gen. Med., 4, 403-412

Colditz, G.A. (2004) Weight Cycling and the Risk of Developing Type 2 Diabetes among Adult Women in the United States. Obesity Res., 12, 267-274.

Corcoran, M.P. et al., (2007). Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. Am. J. Clin. Nutr., 85, 662-677.

De Giorgio, R. & Camilleri, M. (2004). Human enteric neuropathies: morphology and molecular pathology. Neurogastroenterol. Motil., 16, 515-531.

Dinan,T.G. et al. (2006). Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology, 130, 304-311.

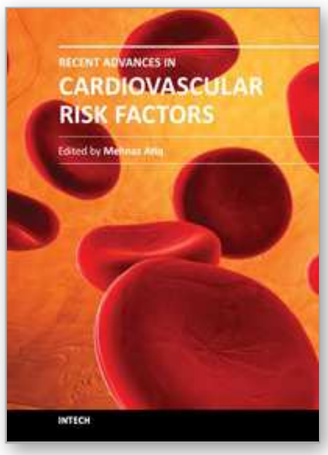
Festa, A. et al. (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation, 102, 42–47.

Flaa, A. et al. (2008). Does sympathoadrenal activity predict changes in body fat? An 18-y follow-up study. Am. J. Clin. Nutr., 87, 1596-1601.

Gershon, M.D., (1999). Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. Aliment. Pharmacol. Ther., 13(Suppl 2), 15-30.

Harshaw, C. (2008). Alimentary epigenetics: A developmental psychobiological systems view of the perception of hunger, thirst and satiety. Developmental Review, 28, 541-569.

Kahna, R. et al. (2005). The metabolic syndrome (Correspondence). Lancet, 366, 1921-1922.
Kinugasa, T. et al. (2000). Claudins regulate the intestinal barrier in response to immune mediators. Gastroenterology, 118, 1001-1011.
Kylin, E. (1923). Studien ueber Hypertonie-Hyperglykamie-Hyperurikamie syndrome., Zentralblatt fur innere Medizin, 44.
Lal, S. et al. (2001). Vagal afferent responses to fatty acids of different chain length in the rat., Am. J. Physiol. Gastrointest. Liver Physiol. 281, G907-G915.
Mather, K. & Verma, S. (2005). Function determines structure in the vasculature: lessons from insulin resistance. Am. J. Physiol. Regul. Integr. Comp. Physiol., 289, R305-R306.
Matsuda, M. & DeFronzo, R.A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care, 22, 1462–1470,
Moller, D.E. & Flier, G.S. (1991). Insulin resistance—mechanisms, syndromes, and implications. N. Engl. J. Med., 325, 938–948.
Ohman, L. & Simrén, M. (2010). Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat. Rev. Gastroenterol. Hepatol., 7,163-173.
Perez PF et al. (2007). Bacterial Imprinting of the Neonatal Immune System: Lessons From Maternal Cells? Pediatrics, 119, e724-e732.
Rana, S.V., (2009). Role of serotonin in gastrointestinal motility and irritable bowel syndrome. Clin. Chim. Acta., 403, 47-55.
Randle, P.J. et al. (1963). The glucose-fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet, 93, 785-789.
Robbins, T.W. & Fray, P.J. (1980). Stress induced eating: fact, fiction or misunderstanding? Appetite, 1, 103-133.
Reaven, G.M. (2006). The metabolic syndrome: is this diagnosis necessary? Am. J. Clin. Nutr., 83, 1237–1247.
Sand, E. et al. (2009). Mast cells reduce survival of myenteric neurons in culture. Neuropharmacology, 56, 522-30.
Singer, D.E. et al. (1992). Association of HbA(1c) with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. Diabetes, 41, 202–208.
Spiller, R. (2008). Serotonin and GI clinical disorders. Neuropharmacology, 55, 1072-1080.
Tirosh, A. et al. (2005). Normal Fasting Plasma Glucose Levels and Type 2 Diabetes in Young Men. N. Engl. J. Med., 353, 1454-1462.
Tornblom, H. et al. (2002). Full-thickness biopsy of jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology, 123, 1972-1979.
van den Wijngaard, R.M. et al. (2010). Peripheral relays in stress-induced activation of visceral afferents in the gut. Auton. Neurosci.,153, 99-105.
van der Waaij, L. A. et al. (1996). In vivo IgA coating of anaerobic bacteria in human faeces. Gut, 38, 348-354
Wang, H. et al. (2003). Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature, 421, 384-388.
Weiss, M.D. et al. (2004). Obesity and the Metabolic Syndrome in Children and Adolescents. N Engl J Med, 350, 2362-2374.
Wiesli, P. et al. (2004). Islet secretory capacity determines glucose homoeostasis in the face of insulin resistance. Swiss Medical Weekly, 134, 37-38, 559–564.
Zwaigenbaum, L. et al. (1999). Highly somatizing young adolescents and the risk of depression. Pediatrics, 103, 1203-1209.



Recent Advances in Cardiovascular Risk Factors

Edited by Prof. Mehnaz Atiq

ISBN 978-953-51-0321-9
Hard cover, 522 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen