Building a Culture of Healthy Nutrition with prevention of Overall Inflammation, Functional Disorders, Vascular Risks and Malignancies

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List of Terms and Abbreviations

BG : Blood Glucose, an index of energy availability in blood for the whole body
IH : Initial Hunger consists of gastric pangs or mind or physical weakness: Inedia is the Italian word for this weakness. In sedentary adults and in children, IH corresponds to 76.6 ± 3.7 mg/dL BG. In infancy corresponds to demand before sight of food.
IHMP : Initial Hunger Meal Pattern: Energy intake is adjusted to three arousals of IH per day.
OGTT : Oral Glucose Tolerance Test
AUC : Area Under Curve of GTT
MBG : The mean of 21 BG measurements before the three main daily meals reported by a week diary. MBG measures the compliance with IHMP, MBG shows changes after training and it is negatively correlated to insulin sensitivity. Below 81.8 mg/dL (Low MBG) MBG indicates a healthy meal pattern in sedentary people. Over 81.8 mg/dL, High MBG is associated with fattening/insulin resistance.

Introduction

Since 1980, the global prevalence of obesity has doubled [1]. In 2015, overweight and obesity accounted for 4 million deaths worldwide, including 3.3 million from cardiovascular diseases and Type 2 Diabetes (T2D) [1]. Restricting energy intake by reducing food consumption, increasing satiety and/or fat malabsorption, is the chief weight-loss mechanism of most medical and surgical treatments of obesity and has profound anti-diabetic effects [2-5]. Increasing exercise- and non-exercise activity-related thermogenesis is the other cornerstone of obesity and T2D management. Simultaneously targeting multiple mechanisms of energy homeostasis is advantageous for the treatment of obesity [6,7]. Targeting meal by meal energy balance has produced a mean 30% decrease of energy intake [6,7]. This lower intake might be useful to current treatments for obesity, T2D as well as to suppress overall inflammation and associated diseases

High Energy Availability

The Paediatric Gastroenterology Unit of the University of Florence had the opportunity of starting a Culture of energy homeostasis during the sixties [6,7]. Mothers brought infants with persistent diarrhoea to the Unit. Those who also had malnutrition were excluded, because this condition suggested the presence of coeliac disease or other inborn errors or defects. In animal experiments and in infants, we varied the energy availability by changes in environmental temperature and maintaining constant energy intake. Low temperature decreased energy availability by increasing metabolic rate. High environmental temperature instead elevated energy availability. At that time, xylose was commonly used to estimate absorption rate. Absorption was measured by the intestinal difference between input and remanence in experimental animals. In human’s absorption was assessed by xylose urinary excretion rate. In these experiments, high energy availability in blood was associated with decreased intestinal absorption rate (FigureS 1,2) [6-10].
Infants

The infants recruited for these experiments differed from the normal anthropometric reference (USA, NIH). Recruited infants had a thin arm skinfold up to the seventh year of age. The increase in energy administration increased BG, insulin resistance, overall inflammation and Resting Metabolic Rate but not weight or skinfold thickness in children with relapsing diarrhoea [11]. The children were examined at the age of 6 - 7 years, when they were well [12-14]. Differences in body weight and in height growth in dependence of high energy intake, emerged after the seventh year of life [12,13].

Normal adults

In investigations on adults before any treatment, one third was insulin sensitive and did not change body weight, energy intake, blood glucose and Resting Metabolic Rate (RMR) after instruction on use of Initial Hunger (IH) and limiting energy intake [6,7,15,16]. This group might spontaneously have chosen a culture of health. Their free, spontaneous maintenance of intake limitations like subjects after adoption of IHMP suggests that this training may be easily acquired. The other two thirds of adults reduced intake and significantly improved their insulin sensitivity after the mentioned instructions and after learning the importance of meal timing.

Pathogenic Mechanism

In the recruited infants and diarrhoeic adults, food administration increased after suppression of symptoms, and diarrhoea frequently relapsed. The relapses were attributed to insufficient or delayed absorption of excessive administration of energy or to high energy availability in blood from previous meals. Skip or delaying one meal was often sufficient to overcome the excess with no symptom relapse. The excess nutrient availability slows absorption, promotes bacteria overgrowth of immunogenic species, mucosal inflammation, diarrhoea relapse [17-24] on one hand and overall pro-inflammatory state in the body [14-20]. The diarrheic state and its pathogenic factors are spontaneously reversible most of the times but not always, about 5% of relapsing infants develop malnutrition [14]. The pro-inflammatory state is associated also with headache, abdominal pain, joint pain, allergy and asthma, eczema, acne, vascular damages and vascular risks [14-24]. The Unit decided the intake strategy on available information about intestinal physiopathology. About 60 % of body immune cells reside just in small intestine mucosa [18]. These cells contrast local bacterial growth during food persistence in bowel. Most intestinal bacteria do not interact with mucosa, in the small and large intestine are always present a number of species that can stimulate inflammatory responses. We evaluate that the number of immunogenic species is between 10 and 100 among a total of 1000 bacterial species that have been identified in small and large intestine. Persistence for years of slow absorption produced damage by bacteria proliferation during increased energy availability [17]. In animal experiments, an increase of thousand times has been seen in duodenal bacteria number [17-20]. We had to administer less food than the maximal amount that the infant was capable of intake. Only after the presumed exhaustion of the previous meal from small intestine, we allowed the caregiver to administer a new meal. The presumption of exhaustion was based on the passage of time from previous meal. After two - three hours or more, demand by the infant, crying often, signalled the emptiness [7]. We named this way of eating as Initial Hunger Meal Pattern (IHMP). Infants adopted this pattern, lost diarrhoea relapses and grew normally like controls. This normal growth was an important achievement and it indicates that an energy intake that allows one or more events of perception of hunger per day allows also good growth in infants and presumably normal functions [6-7] in all
children and adults. This implication does not mean that habits to prolonged hunger are safe. We never starved healthy children or adults asking for food.

An important moment of decisions about intake happens soon after birth. New mothers do not make difference on food administration between at scheduled meal time versus after demand. We demonstrated that conditioned, scheduled intake sustains fattening, insulin resistance and the associated immune depression (sterile inflammation) [2-5,15-24]. The optimal intake corresponded to a fixed LBG level before meals (76.6±3.7 mg/dL for sedentary people) that can be easily maintained after learning the correspondence between sensations and BG before meals (Initial Hunger). A consistent minority maintains the LBG level by free choice, before any training in IHMP.

**Energy Availability**

Energy availability was assessed by using Blood Glucose (BG) as an index. We prevent too low availability to better allow body functions and every activity. Also, too high availability is detrimental by generating unwanted reflexes. Absorption becomes slow (FigureS 1,2), and the slowing provide more nutrient to bacteria in intestine [9-11]. Bacteria overgrowth implies an increase in the number of immunogenic species. One or two species from about ten to 100 (immunogenic) species reach an excess number, over 10^3 per gram of content. This amount can induce inflammation in human intestine [18-20]. The inflammation does not remain limited in the mucosa; it invades blood and all body (subclinical inflammation) [6,7]. We showed an association between high energy availability and functional disorders [6,7,11-15].

At recruitment, the investigated population presents individuals that have mixed levels of energy availability [6,7]. We assess this energy availability by blood glucose. BG values are correlated to other macronutrients and BG is burnt out before other nutrients. Omega three fatty acids circulate in blood after other nutrients providing nutrients. The individual meal pattern in a time period, during a week e.g., can be assessed by Mean Blood Preprandial Glucose (MBG) that is measured 21 times, i.e., before three main meals in a week. We found that each recruited toddler and recruited adult had his own individual MBG and maintained the personal MBG with modest variation. The confidence interval within a week was 3.8 mg/dL around diary mean [7]. The MBG informed on the habitual metabolic condition (energy availability and balance) in different times, with different diets and in different individuals. In case of divergence between estimation and portable measurement, mothers followed estimation. Thus, the subject’s meal pattern is guided by his/her aim for having a definite, constant flux of available energy. Subjects or parents measured capillary blood by glucometer (a portable potentiometer for whole blood glucose measurement: Glucocard Memory; Menarini Diagnostics; Florence, Italy) in the quarter-of-an-hour before they intended to take a meal.

**Cancer**

The association between energy intake and malignancy development is well known in experimental animals with inherited predisposition to malignancy for 50 years [1-5]. Prevention of inherited tumors was obtained in these animals by a mean 30%, lifelong decrease in energy intake [1]. Up to recent days, 30% lifelong decrease of energy intake seemed as an intolerable coercion in humans. Man seems happy of having achieved a decrease in prevalence and severity of infarctions and does not hope in a complete elimination. This intermediate solution is poorly appealing for malignancies. Man cannot become happy for prolonging life by allowing the development of a malignant tumor. The appealing difference lays in getting free from tumor instead of living longer with tumor development. Intake control provides prevention although healthy people do not like energy intake controlling. Yet, getting free from malignancy is so important to allow great investment and individual engagement.

**Cancer is a Disease of the Genome**

In many tissues, there are numerous small and inconspicuous neoplastic lesions that rarely become overt cancers [2-4]. In these small lesions, clonality and oncogenic mutations have been identified. These lesions include established benign tumours such as melanocytic nevi and even groups of cells that are histologically only marginally abnormal. Once they have grown to a certain size, such lesions stop growing appreciably and do not become more aggressive over many years or even decades [3,4]. For instance, few moles, which are benign tumours of cutaneous melanocytes, grow larger than 1 cm, and fewer than 1 per 1000 ever progresses to melanoma. In this condition, increase in cell reproduction multiplies abnormal mutations. More than half body immune cells are located in the intestinal mucosa. Hundreds of trillions of viable bacteria provide the antigens from intestine. Malignant developments arise through many years and decades of maintenance of a situation of multiplied cell replication. Conditioned intake promotes 15% increase in Resting Metabolic Expenditure (RMR) and an increase of about 30% energy intake [24] (Tables 1,2). Results on glycated haemoglobin mirror those on insulin [7]. The increase in energy availability is associated with insulin resistance and a diffuse inflammatory condition [2-5]. This inflammatory state increases destruction of immune and also tissue cells in all body. DNA reproduction also increases. Every cell reproduction may become an occasion of abnormal mutation [2-5].
Johnson says the mechanisms linking diet to cancer “can be understood and exploited” for both prevention and treatment, and he points to several “scientific and strategic reasons to focus such research on carcinomas of the alimentary tract.” The March 25, 2005 issue of the journal Science contains an editorial by Ian T. Johnson, head of the Gastrointestinal Biology and Health Programme at the Biological Sciences Research Council in the UK, that explores the abundant yet largely unknown microorganisms in human intestine, their normal functions of digestion and delivery of nutrients, and the diseases to which it is prone [11,21,24]. In his editorial, “Cancers of the Gut and Western Ills,” states that despite the huge progress made in understanding the molecular basis of many cancers in recent years, “Most of the new knowledge has been deployed in the search for new therapies rather than to understand the role of nutrition in their causation.” Johnson says the mechanisms linking diet to cancer “can be understood and exploited” for both prevention and treatment, and he points to several “scientific and strategic reasons to focus such research on carcinomas of the alimentary tract.” These include evidence in support of “Over nutrition” as a factor in an increased risk of bowel cancer within population of the developed world that shows overconsumption of energy, low levels of physical activity, high body mass index, and abdominal obesity. He also notes evidence for a link between obesity and esophageal cancer, once rare “but now advancing rapidly throughout North America and Western Europe.” Johnson sees “Little evidence” to support the view that alimentary cancers are tied to the adverse effects in the diet of food-borne carcinogens, despite the presence of mutagens in low concentrations in foods and feces. “It seems more plausible that the Western gut become vulnerable to neoplasia because of adverse metabolic factors, such as pro-inflammatory enzymes in precancerous tissues, and because of low intakes of anti-carcinogens from plant foods.” He asserts that the role of weight, lack of exercise, and inadequate consumption of plant foods in the etiology of gut cancers “needs to be more widely acknowledged and publicized.” Also included in this issue of Science is a report from Johns Hopkins University...
School of Medicine, the National Institute on Aging, and Keio University School of Medicine in Tokyo, Japan, that suggests a cellular mechanism by which epigenetic alterations in normal cells may affect cancer risk. In the study, loss of imprinting of the insulin-like growth factor II gene is tied to alterations in intestinal maturation and tumorigenesis in mice. Altered maturation of non-neoplastic tissue may be one mechanism by which epigenetic changes affect cancer risk [25-28].

These opinions are supported by the inflammatory developments that are now well known and are strongly associated with the conditions of insulin resistance and diabetes [17-20]. These conditions are widespread like the conditioned eating that seems as natural. Current society promotes diabetes since the first new born meals by food offering: scheduled meals are considered normal custom for educated societies [7,11,22,23]. Infant/mother pairs recognize easily IH without BG measurements [7,11,24]. Adults can learn the recognition in few days, and meals allowing three IH arousals per day are associated with an even energy balance and diabetes prevention [11]. This meal pattern may become the reference for normal energy intake and for normal/ideal bodyweight.

We elaborated the enclosed protocol to limit intake and stop diarrhoea recurrences [6,7,11]. The diarrheic recurrences were attributed to excess energy intake. Thus, the protocol is finalized to a homeostatic biological condition as regards energy availability and body weight. The homeostatic energy availability is associated with lower immune stimulation. The protocol suggests to let arise hunger by suspending intake and to recognize this type of hunger before taking any meal. Sometimes, this hunger arose too lately. Intake reduction of energy dense food items promptly anticipated hunger arousal. On the other hand, a subject who recognizes to have no hunger cannot complain about missed intake and his/her attention easily migrates on every working, playing and other activities. Hunger, even intense and disturbing may emerge if conditioned, but this event may be recognized, and attention may be diverted from food.

IHMP

We obtained meal-by-meal fasting nutrient levels (low BG) prior to the next meal and suppressed fattening/insulin resistance. This pattern has been termed the Initial Hunger Meal Pattern (IHMP). Ignoring Initial Hunger contributes to increase obesity and diabetes in adults and in children. In the last half century, not only obesity and diabetes have increased in children but also asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, schizophrenia [29]. IHMP and minimal bacteria growth in the alimentary canal might become a strategy for health. The purpose of this strategy is to reduce the mentioned increases, as well as to reduce functional disorders, vascular and malignant diseases, diabetes. The vascular involvement suggests an effect on Alzheimer disease [30].

Training Protocol

- Suspend meals for up to 48 hours
- Locate physical sensation of hunger
- Measure blood glucose concentration (BG)
- Mentally associate the physical sensation with the BG concentration
- Begin with a meal of about 300 kcal
- Repeat 1-5 increasing the meal size in proportion to the desired interval
- Repeat the above procedure for two weeks. At each arousal of physical hunger, compare the aroused sensation and the measured BG with the initial ones at intervention beginning.

Conclusion

After training, a consistent part of investigated adults or toddler-mother pairs maintained the energy intake that they had already low at recruitment [6-7]. The two (Tables 1,2) show the mean effects in the entire group. After five months, suppression of conditioned intake is associated with mean decreases of 30% energy intake, of 15% blood glucose, 15% RMR, 30% insulin resistance, of up to 10% body weight and elimination of associated overall inflammation. Confirmation of these results is feasible in follow up studies between trained and control cohorts. These achievements and the training protocol are unknown in the Western Countries, but both may be implemented directly by lay people with the only encouragement of physicians. Quousque tandem these facts and associations shall remain unknown?

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References


