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Editorial

Immunogenic Bacteria

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Abstract

Minimal bacteria growth on small intestinal mucosa is associated with prompt absorption of food, as happens during insulin sensitivity. Any meal by meal excess intake over expenditure (insulin resistance) fosters microflora growth and sort of reversible immune deficiency (subclinical inflammation, overall inflammatory state, or pro-inflammatory state). Overweight is the cumulative result of meal by meal positive balance. Fattening increase both insulin resistance and overall subclinical inflammation. A weight stable is poorly effective on subclinical inflammation, and weight decrease diminishes the overall inflammation. In the small intestine, unabsorbed food becomes harmful to mucosa and all the body for the existence of bacteria in the intestinal lumen and the possibility of an active proliferation inside the lumen until food is available. On the contrary, rearing experimental animals without bacteria reduced to 10% cellular infiltration and immunoglobulin production in small intestine mucosa.

Keywords: Minimal Bacteria Growth; Intestinal Mucosa; Insulin

Introduction

Physicians and patients expect that a gastroenterologist suggests some food that solves clinical problems. Although seemingly far from clinical solution, pathophysiology is the key to solve all issues. The pathogenesis is rather constant in presence of allergy, bacteria and viruses. Minimal bacteria growth and minimal immune stimulation on small intestinal mucosa are associated with prompt absorption of food, as well as insulin sensitivity [1-99]. The meal may be increased over expenditure up to a mean 15.5% in absence of weight increase [40]. Any excess over this intake progressively increases insulin resistance, slowdown in nutrient absorption and fosters microflora growth as well as reversible immune deficiency (subclinical inflammation, overall inflammatory state, or pro-inflammatory state) [3-99]. Overweight is the cumulative result of meal by meal positive balance. Weight increase and fattening produce an increase in insulin resistance and RID. A weight stable is poorly effective on subclinical inflammation, and weight decreases diminish the overall inflammation. In the small intestine, unabsorbed food becomes harmful to mucosa and all the body for the existence of bacteria in the intestinal lumen and the possibility of an active proliferation inside the lumen until food is locally available [68]. On the contrary, rearing experimental animals without bacteria reduced to 10% cellular infiltration and immunoglobulin production in small intestine mucosa [70]. Tropical enteropathy exhibits a denser infiltrate than European and American normal mucosa in dependence on absorption slowdown in a warm and humid climate.

The conception of intestinal saprophytes was rather naïve. Bacteria grow in the colon and everywhere in dependence of water, ammonia and available nutrients and temperature. Water is freely available on mucosal surfaces, and nutrients (carbohydrates, proteins) depend on eating and more precisely on current energy balance. We compared the xylose absorption rate in two groups of experimental animals, one at the environmental temperature of

30°C and the other at 6°C environmental temperature [59]. At high environmental temperature, the absorption rate halved in comparison to animals kept at low temperature. We obtained similar results in humans [60]. A slowdown of metabolic and absorption rates explain unexpected microflora growth [59-64]. Bacteria in the colon double every day, very slowly in comparison with growth in the small intestine, where bacteria can double every 15 minutes [68]. Bacteria obtain little energy from non-absorbable, indigestible fibers in absence of oxygen. All meat, bread and most energy dense meal component do not arrive to the colon. These highly energetic foods would promote an explosive growth. The rumen is similar to the human colon in hosting bacteria in an ambient that has poor nutrients and is absolutely devoid of oxygen. Energy rich nutrients let develop one – two liters of carbodioxid per minute in the rumen. The small intestine is also anaerobic, and oxygen absence increases toward the end of the intestine. 60% of bacteria do not stimulate any immune response [69]. 10% - 15% evoke a response by IgG, lymphocytes and neutrophils that are destructive on invading bacteria, mucosa and overall in the body during subclinical inflammation. Minimal bacteria growth requires minimal persistence of nutrients in the small intestine lumen like on teeth. This depends on intake amount and rhythm. Amounts and intervals can be externally decided by doctors, who apply standard international averages from healthy people. Any decision about eating start, the amount and any stop may better be taken by the subject's estimation of personal cues on the personal energy balance [52,53]. Hunger has been shown that can be taught [100]. Learning the prediction of energy availability and balance has been shown [39-42]. The suspension of food administration to a healthy baby with functional bowel disorders provoked crying for hunger (Initial Hunger, IH) within 48 hours of time [39, 40]. This cue was subjective although being more certain than any laboratory measure. As pediatricians, we provisionally assumed that crying for hunger corresponded to initial emptiness of stomach and small intestine and to the time of most active absorption [39,40]. The administration amount might correspond to expenditure in the interval between subsequent similar meal demands. This correspondence is exact in the long (monthly) period. Insulin resistance may sometimes arise independently from eating, like during psychological stress and fever.

A transient break in eating is useful in these events that are associated with insulin resistance. Although the energy expenditure increases and body energy balance is negative during fever, preprandial BG remains high, and the balance in blood is positive for energy influx from fat stores [71-73]. We consider this divergence between intake and expenditure as acceptable and normal. Hormones that allow the body to meet stress such as cortisol, cortisol releasing factor, and serotonin together raise blood glucose concentration, activate mast cells, monocytes, and macrophages, increase intestinal permeability, and contribute to subclinical inflammation – essentially the same effects as eating in the absence of IH. Suspension of meals for one three days is accepted. Yet the balance problem becomes difficult when a stressful condition (anxiety) persists for weeks [1,2].

Positive energy imbalance and microflora overgrowth

The maintenance of inflammation is much more pronounced in the mucosa of the small intestine than in that of the colon. The more intense conflict against the luminal content may depend on the surface area that has been estimated as high as 10,000 square meters in the small intestine. The colon surface is devoid of villi and microvilli and may be about one square meter. One – two percent of big molecules in the lumen cross the small intestine epithelium, and exercises an immune stimulation inside the mucosa. For poorly known reasons, bacteria exert immune stimulation more than food [70]. We insist that bacteria multiply in dependence on nutrients availability, mainly on energy and iron. The host supplies ammonium for bacterial proteins. Minimal bacteria growth on the mucosa is a necessary step to achieve health, like on the periodontal mucosa. During positive energy imbalance, the small intestinal absorption slows down; intestinal microflora grows and produces an increase in the inflammatory infiltrate in the small intestine and reversible functional derangements [65-70]. In experimental animals, we have described an increase of inflammatory cells in the mucosa after administration of broth culture containing not pathogenic *Escherichia coli* [75-77]. This bacterium was not a pathogen, but elicited an inflammatory response, as an immunogenic component of intestinal microflora. We showed an increase in bacteria number in biopsies of children during absorption and a decrease

in bacteria number in time after the last meal [70-72]. Subjects with irritable bowel syndrome (in infancy, chronic nonspecific diarrhea) actually show an increase in mucosal inflammatory cells [78-84]. A suspension or a decrease in intake cured these diarrheic toddlers by subtracting nutrients to mucosal microflora. Decrease in insulin resistance and in overall inflammation might have influenced the recovery.

Immune involvement

In our laboratory hypothesis, each meal carries on a battle. Every meal renews or reignites the never ending conflict between bacteria growing on mucosa and immune reaction. Sometimes the conflict is acute and raises symptoms, more often damages all body although progressing without any awareness (overall subclinical inflammation). Bacteria double every 10 - 20 minutes in the small intestinal nutrients [60-64,78-96]. The mucosa of the small intestine hosts half the body production of immune cells and sustains a permanent moderate local inflammation, consisting of IgA and phagocytic responses, "tolerant" inflammation [97-100]. About one hundred commensal bacteria are immunogenic in the human intestine [69]. An increase in this bacterial growth to about one billion per gram of mucosa provokes increase in production of lymphocyte and of IgG antibodies and reactions with mucosal damages [75-89]. Antigens and activated monocytes are discharged from circulation producing (or worsening) a local inflammation and a subclinical inflammation throughout the body [1-25,97-101]. This inflammation has received many names: overall inflammation, proinflammatory state and Reversible Immune Deficiency [2]. We preferred these two last names to emphasize the detrimental, immune involvement of the entire body from meal energy intakes that are unbalanced by correspondent high energy expenditure. This immune involvement increases and prolongs all localized inflammations and worsens general diseases [1-25,97-100]. The suppression of the immune stimulation of intestinal mucosa was the strategy for a new life, for recovery from infection, from immune illnesses and from malnutrition as well as from obesity and to prevent risks and deterioration for everybody. Short absorption times (two – three hours) alternated with periods of emptiness may achieve this goal.

Overall subclinical inflammation

"Insulin resistance" is associated with a "pro-inflammatory state" or "subclinical inflammation", and the association is supported by a huge amount of research [1-100]. The findings of this association represent a high achievement in understanding human nutrition and health. The general acceptance of this association took unfortunately 80 years [22-25]. Persistent unbalanced energy intake and/or psychophysical stresses modify the activity of monocytes, macrophages and mast cells, and together alter the neuro-endocrine system [1-25]. These disorders increase intestinal permeability [95]. Bacterial biofilms may develop inside the alimentary canal and produce endotoxins that invade blood and all tissues. Immunogenic bacteria induce a huge biological pressure on human immune system and deep functional alterations. The invasion of body tissues by bacterial products and endotoxins sustains subclinical inflammation and causes the slow progression of many chronic diseases like asthma and rheumatoid arthritis. Thus, body tissues develop a pro-inflammatory state (subclinical inflammation, a synonym) that is sterile, ineffective and dangerous for body tissues in the intestine and elsewhere.

Health as minimal immune stimulation

Abundance of nutrients can start e cascade of reflexes in the alimentary canal. Slowdown of absorption and microflora overgrowth raise the causal chain between intake and subclinical inflammation, functional disorders, deterioration, vascular risks, increased cell turnover and development of malignancies. The nutrient abundance just coincides with insulin resistance and fattening, two events that are associated even when appear alone. The absorption slowdown coincides with the condition of insulin resistance. In animal experiments, insulin infusion into portal vein increased intestinal absorption rate [80]. After a similar intake, we found a decrease in the absorption rate in a warm environment in comparison with a cold environment in both animal and human experiments [59,60,72]. The cold environment is associated with higher energy expenditure than the warm one [61]. The increase in energy expenditure decreases insulin resistance [62-64].

Another absorption slowdown develops during infection and inflammation [71]. We conclude that healthy nutrition coincides with insulin sensitivity, whereas slow absorption and subclinical inflammation develop during an increase in insulin resistance. In our studies, disordered bacteria growth on intestinal mucosa and overall subclinical inflammation are due to a unifying pathogenic factor, insulin resistance

Who may be interested?

We encountered two opposed criticisms. Conservative Nutrition authorities sustain that dieticians already suggest hunger sensations as a prerequisite for meal. The other criticism is that expressed by simple patients. A too severe regime the waiting for arousal of hunger to get meals! The two criticisms are mutually destructive. In hunger recognition, untrained, control people compare current, conditioned sensations with the usual aim for certain energy availability. This aim develops within ± 3.8 mg/dL of blood glucose [41,42]. Hunger sensations may be as powerful as after eating suspension. Hunger recognized by untrained control does not differ from previous, conditioned pre-meal sensations. Trained IH is instead constantly associated with a low BG. Preprandial signaling meals by IH is moreover associated with decreases in GTT AUC, in Hba1c, in measurements by doubly labeled water and by indirect calorimetry, not to mention with decreases in measurements of weight and skinfold thickness!

In the first days of life, mothers have no difficulty in the acceptance of feeding their newborns on demand to prevent overweight and diabetes in subsequent ages [39]. Centers for diabetes treatment may embrace Hunger Recognition and associated increase in insulin sensitivity to prevent body weight increase, as an adjuvant or substitute for insulin and similar drugs. Facing ill human beings, physicians may distinguish when any intake excess over expenditure increases immunogenic bacteria in the small intestine and reduces immune defenses efficiency. This predictive role remains as an always useful skill for any physician.

We consider "Culture" as an increase in being aware of effects by own personal acts. A general improvement of this increase is expected by "*Homo sapiens*" in the next years and centuries. Yet business may transiently prevail and substitute this improvement. An orientation of the meal pattern along the guidelines suggested in these papers [41,56,57] may remain in the hands of isolated doctors and scientists, and spread slowly.

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