Microbiota and Obesity

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Abstract

Obesity is globally the most prevalent nutritional disorder. Multifaceted therapeutic approaches are called for to halt the cascade from neonatal adiposity/high birth weight to childhood excessive weight gain/adult obesity with comorbidities. Recent experimental and clinical data provide one new target for interventions aiming to close this vicious circle: the microbiota. An aberrant gut microbiota, dysbiosis, induces immune and metabolic disturbances both locally and, consequent upon impaired gut barrier function, also systemic low-grade inflammation, which is causally linked to insulin resistance. The gut microecology could thus fill the gap between energy intake and expenditure by processing nutrients and regulating their access to and storage in the body, producing chemicals of hormonal nature and controlling the secretion of proinflammatory mediators locally and systemically. Conversely, being highly sensitive to environmental impacts, particularly to early feeding, the compositional development of the gut microbiota may prove the target of choice in efforts to reduce the risk of obesity. It has been demonstrated that a lower number of bifidobacteria precedes the development of obesity, and a dearth of butyrate-producing bacteria and an overall richness of bacteria increase the risk of metabolic disease; moreover, recognition that practices known to disrupt the early gut microbiota, e.g., cesarean section delivery and antibiotic exposure, contribute to obesity, encourages to pursue this line of research.

Obesity – The Epidemic

Concurrently with important advances in medicine, the burden of obesity has become a plague of our times; whether the link is causal remains elusive. Obesity is the common denominator of diet-related chronic disorders such as cardiovascular disease and diabetes, but also chronic inflammatory and allergic diseases. Indeed, overweight and obesity can be seen as belonging to the family
of noncommunicable diseases sharing common environmental risk factors and immunologic features, which frequently coexist and constitute a threat to human well-being. Somewhat belatedly, the list of entwining conditions now extends to mood and brain, wired to the gut by means of bidirectional exchange of endocrine and immune and neural signals.

Obesity is globally the most prevalent nutritional disorder among children. Two decades ago, the World Health Organization declared obesity a global epidemic [1]. The term defines groups of cases resembling each other and, secondly, groups of different diseases occurring in the same place or in the same season and sometimes spreading “on (epi) the people (demos)”, in contrast to nosos, a term used to describe diseases at individual level [2].

The NCD Risk Factor Collaboration found that the mean age-corrected body mass index (kg/m²) has continued to increase in men and women alike, exceeding 24 in both, in 200 countries and territories between 1975 and 2014 [3]. During this period, the risk of becoming obese was higher than that of being underweight. The obesity epidemic is thus a moving target, and a solution is both challenging and urgent. The velocity of propagation of the epidemic is high in children and young adults of reproductive age with the potential to transmit the propensity to the next generation [4]. The risk of escalation of the problem should be given high priority in health policy, and prevention is better than cure.

**The Microbiota: Origin and Potential in Reducing the Obesity Risk**

The hygiene hypothesis suggests that environmental changes in the industrialized world have led to reduced microbial contact at an early age and thus contributed to the epidemic of atopic disease [reviewed in 5]. In 1976, Gerrard et al. [5] found an inverse relationship between the incidence of infections and atopic disease and concluded that a relative freedom from diseases due to viruses, bacteria, and helminths caused the latter. Again, in 1989, Strachan [6] detected an inverse correlation between family size and the prevalence of allergic rhinitis and suggested that infections acquired from older siblings might confer protection against the development of atopic disease.

An extended version of the hygiene hypothesis has since been introduced [7] to underscore the intimate interrelationship between the immune system and the microbiota and link their united forces to the theory of developmental origins of health and disease [8]. Accordingly, the risk of noncommunicable diseases is heightened if the environmental conditions after birth differ from those experienced by the fetus during pregnancy. Epidemiological data corroborate the importance of stable pre- and postnatal nutrition: restricted in utero...
nutrition followed by the abundant supply of nutrition in the Western lifestyle increases susceptibility to metabolic disorders [9]. Clinical evidence, again, points to both maternal under- and overnutrition in pregnancy as equally inductive of an obesity risk in the child [reviewed in 4, 10].

This concept may be extrapolated from nutrition to the host-microbe interaction. Undeniably, modern techniques have generated a microbiome renaissance, and the forgotten organ is now given the attention its size and impact deserves, particularly during the critical period of programming. In fact, microbe contact in the perinatal period represents the most massive antigen exposure educating the physiological adaptation processes to the anticipated postnatal environment. The newborn lacking an age-appropriate and environment-adjusted microbe contact optimal for timely maturation of the immune, metabolic, and neural regulatory systems may be predisposed to develop allergic disease, chronic inflammatory conditions, and obesity (Fig. 1).

The extended hygiene hypothesis calls for a prudent review of clinical practices, which may interfere with the healthy host-microbe interaction during the critical period within which, according to the developmental origins of the health and disease theory, the immune and metabolic phenotype is consolidated (Fig. 1). These practices include delivery by cesarean section and antibiotic use. Elective cesarean section accompanied by antibiotic treatment hinders the establishment of the gut microbiota more or less transiently but nonetheless carries long-term clinical consequences manifested as immune-inflammatory conditions as well as obesity [11]. The impact of maternal obesity may still constitute

**Fig. 1.** A schematic presentation of the proposed relationship between the gut microbiota and early environment and nutrition, which underlie the risk of noncommunicable diseases in childhood.
a confounder here. A recent systematic review and meta-analysis, however, has demonstrated that cesarean section exerts an independent effect on obesity in children, even when the results were adjusted for maternal prepregnancy weight [12]. Epidemiological data linking early antibiotic exposure to a later obesity risk are more conflicting. One potential explanation might be sought in the limitations of register data, retrospective or large cohort studies, or epidemiological methods of evaluating interactions with detailed host characteristics such as diet, health, and prevailing gut microbiota composition. Indeed, antibiotic exposure was shown to exert distinct effects in infants of mothers with a high prepregnancy body mass index as compared to those of normal-weight mothers; antibiotic exposure reduced the risk in the former but increased it in the latter [13].

In point of fact, the rate of cesarean section delivery exceeds the WHO recommendation for nonmedical reasons, and the cumulative trend seems to continue [14]. Conversely, the rate of breastfeeding fails to reach current recommendations; breastfeeding guides the healthy compositional development of gut microbiota postnatally.

Finally, the contribution of mother’s health, weight, and weight gain during pregnancy to the metabolic health and disease risk of the child is recognized as being to a degree determined by the maternal gut and breast milk microbiota [11]. Indeed, the composition of the gut microbiota through pregnancy and within breast milk is not standard, but evinces marked individual variation [15]. These sources provide the inoculum for the establishment of the gut microbiota in the newborn. Different routes may communicate aberrancies in the mother’s microbiota composition during pregnancy, at delivery via microbes in the mother’s birth canal, and in close contact with the mother and her immediate environment after delivery [reviewed in 4].

One attractive idea arising from the unified hypothesis, the extended hygiene hypothesis linked to the developmental origins of health and disease theory, is modification of the maternal gut microbiota during pregnancy and the perinatal period, as well as the breast milk microbiota. Promoting a balanced host-microbe interaction may aid in attuning the child’s gut microbiota to age and reprogramming the risk of chronic inflammatory conditions, including obesity.

**Microbiota Functions in Metabolic Health**

In light of the energy balance equation, obesity development appears straightforward: energy intake exceeds that expended. Indeed, the energy nutrients consumed excessively in the current sedentary Western lifestyle has been seen as the
source of the obesity epidemic. Replacement of energy nutrients, however, by noncaloric substitutes has not provided a solution but may indeed have contributed to the obesity epidemic, emphasizing the multilayered mechanisms of nutrition-related conditions in humans. Simultaneously, the complex collection of the human gut microbiota has failed to adapt to the abundance of modern dietary preferences: a diet rich in fat, sugar, and protein and low in fiber. In fact, the task of the gut microbiota, an instrumental element of host defense, is strengthening of the gut barrier functions, competitive exclusion of pathogens, and alleviation of the intestinal inflammatory response (possibly for the purpose of resisting ancient food-borne infections), and concomitantly aiding in energy extraction and storage from the diet (conceivably to adjust to times of food shortage).

Recent scientific advances tend to challenge earlier reasoning that the gut microbiota functions merely as a barrier component efficient in assimilating antigens encountered by the enteral route. Experimental studies demonstrate that the immune and metabolic deviations involved in obesity may not derive linearly from dietary intake but rather from gut microbiota modifications induced by the diet [reviewed in 4]. Hence, notwithstanding incomplete evidence from clinical intervention studies thus far, the composition of the gut microbiota may be taken to represent a strategic contributor to obesity as it pertains to excessive energy intake from an unhealthy diet and disproportionate storage of energy owing to sedentary behavior.

Gut Microbiota and Obesity Epidemic: Cause, Consequence, or Mechanism?

Scientific interest in the potential causative role of the gut microbiota in obesity was attracted by the demonstration that a distinctive gut microbiota composition prevails in obese individuals, with adjustments following weight gain or weight loss [16]. In the same vein, aberrant compositional development of the gut microbiota is documented during breastfeeding in infants in whom overweight development was documented, i.e. gut microbiota deviation precedes obesity [17]. Further support for the conception of microbiota involvement in obesity is obtained by epidemiological data linking known causes of gut microbiota disturbance early in life, namely cesarean section delivery and antibiotic exposure, to the subsequent development of overweight and obesity [reviewed in 4]. Experimental studies, again, have improved our understanding of mechanisms and causality in this context. Taken together, these elements markedly reinforce the hypothesis that modification of gut microbial communities might offer a strategy applicable to obesity management [18].
The Western diet with its high-fat and -energy content has been associated with reduced gut microbiota diversity and perturbed composition, dysbiosis, an imbalance in the taxonomic composition of the gut microbiota. The gut microbiota impacts on metabolism by retrieving nutrients otherwise inaccessible to the host (Fig. 2). Experimental studies have provided evidence that specific gut microbiota profiles facilitate the extraction of calories from the diet and their storage in the host adipose tissue [19]. These phenomena have been shown to act simultaneously. Dysbiosis may increase energy efficiency via fermentation of nondigested food, thus providing more energy to the host; intestinal monosaccharide absorption and energy extraction as short-chain fatty acid (SCFA) production, combined with subsequent stimulation of de novo synthesis of triglycerides in the liver, boost weight gain. Furthermore, dysbiosis could increase fatty acid storage in adipocytes by suppressing the fasting-induced adipose factor in the gut, which in turn increases enzyme lipoprotein lipase activity in adipocytes and enhances fat storage [19]. A balanced gut microbiota composition, again, protects against diet-induced obesity by inhibition of cellular energy-dependent protein kinase activation [20]. A third potential explanation lies in the
association between SCFA signaling molecule activation and energy storage [21].

The role of SCFAs in enhancing energy efficiency may be more complex than initially anticipated. SCFAs may exert beneficial metabolic effects in adipose tissue and the liver and improve insulin sensitivity. A lower abundance of butyrate-producing bacteria has been associated with an increased metabolic disease risk in humans, as butyrate-producing microbes show an anti-inflammatory potential and alleviation of the metabolic disturbances of obesity. The effect of butyrate on the intestinal barrier is nonetheless paradoxical. Butyrate may promote gut barrier function at a low concentration, while a high concentration may have the opposite effect [22]. Equally, SCFA acetate, produced by specific bifidobacteria, promoted intestinal defense mediated by epithelial cells [reviewed in 23]. Enhanced production of acetate, a substrate to cholesterol and triglyceride synthesis, was observed in experimental animals fed a high-fat diet compared to counterparts on standard diets [24]. Further, acetate was documented to increase, firstly, ghrelin levels and thereby also drive the host to eat excessively, and, secondly, glucose-stimulated insulin secretion. Acetate administration centrally in the brain increased glucose-stimulated insulin secretion, while pancreatic stimulation by acetate failed to accomplish this effect.

Glucose-stimulated insulin secretion proved able to be induced in recipient animals by fecal transplantation from animals on a high-fat diet. Microbiota depletion, in contrast, suppressed acetate turnover and reduced ghrelin levels. SCFA propionate shows a potential to protect against inflammatory responses by lowering fatty acid levels in plasma and to improve host glucose metabolism, unlike SFCA acetate in this experiment model. This distinction points to the site of activation of the parasympathetic nervous system mediated by the vagus nerve: the peripheral nervous system in the case of propionate and the central nervous system in the case of acetate [24]. Indeed, recent proof of gut microbiota involvement in obesity derives from the gut-brain axis, a bi-directional communication between the central nervous system and the gut.

Over and above processing nutrients and regulating their access to and storage in the body, activated inflammatory pathways are a corollary to “obesogenic microbiota” (Fig. 2). Indeed, the demonstration of active inflammatory cascades in the ileum in response to a high-fat diet prior to the onset of obesity invites the notion that the low-grade inflammation of obesity may be initiated in the gut, and specifically by the gut microbiota, the presence of which is a prerequisite in the progression of inflammation. Elevated systemic exposure to lipopolysaccharide, an endotoxin released by gram-negative bacteria, characterizes this inflammatory tone, defined as “metabolic endotoxemia” [25]. Aided by dysbiosis-induced impairment in the gut barrier function, lipopolysaccharides
are delivered to CD14 and toll-like receptor 4, and the ensuing production of preinflammatory cytokines aggravates glucose and insulin metabolism and contributes to the onset of overweight-associated pathologies, including type 2 diabetes, hypertension, hepatic steatosis, and dyslipidemia [reviewed in: 4, 23, 26]. Interestingly, dietary fatty acids, of which circulating levels are often increased in obesity, have previously been shown to induce insulin resistance through the same signaling pathways, linking the nutritional environment to the gut microbiome within the innate immune regulation [23, 26].

**Gut Microbiota Profiles Are Causally Linked to the Obesity Risk**

The most plausible evidence of a causal relationship between dysbiosis and the obesity risk has been obtained from experimental studies demonstrating that gut microbiota transfer from an obese individual can produce the obese phenotype in the recipient [27, 28]. Colonization of germ-free mice with the gut microbiota from an obese mouse or human enables weight gain and fat mass accumulation in these animals, without altered dietary intake. In accordance with this line of experimental work, there are clinical case reports on the treatment of recurrent diarrhea caused by *Clostridium difficile* by fecal transplantation, which demonstrate the development of obesity, the donor metabolic type, in the recipient [29].

It needs to be acknowledged that current demonstrations are far from complete in identifying specific constituents within the “obesogenic microbiota” as causative offending agents in the vicious circle of obesity. Phylum-wide compositional patterns have been shown to differ between obese and lean individuals but with contradictory outcomes [16, 19, 30]. These include reduced microbial diversity and a shift in the relative abundance of *Bacteroidetes* and *Firmicutes* and a higher abundance of *Proteobacteria*. It must also be conceded that different methods and populations and continuously developing techniques hamper direct comparisons among studies.

Data are accumulating, however, to prove the necessary initial step of dysbiosis in obesity, when the gut microbiota is taken as one operator [18]. An important conclusion to be drawn from human studies is that the rate of acquisition of certain microbiota patterns appears crucial for the programming of later health [reviewed in 4]. For example, a lower abundance of bifidobacteria, with specific species present, during the period of exclusive breastfeeding in vaginally delivered infants devoid of antibiotic exposure may predict adiposity [4, 17]. Experimental findings tend to substantiate this clinical finding by connecting high numbers of bifidobacteria with normalization of the inflammatory status and improved glucose tolerance and glucose-induced insulin secretion [31].
Likewise, at an early age, differences in \textit{Bacteroides} group colonization may indicate disadvantaged metabolic health later [32]. Undernourished children in developing countries have exhibited a younger gut microbiota profile than expected for their chronological age [reviewed in: 4, 33], while precocious maturation has been seen in overweight children [34]. Further, the meconium microbiota of infants born to mothers with diabetes mellitus resembles that of an adult diabetic [35]. In adolescents and adults, increased numbers of \textit{Proteobacteria} have been considered characteristic of dysbiosis [reviewed in 18], while \textit{Akkermansia muciniphila}, a member of the \textit{Verrucomicrobia}, may typify control over inflammation and adipose tissue metabolism [36]. In pregnant women, an association between gut microbiota composition and nutritional status has been reported [37], and specifically a gut microbiota profile higher in numbers of \textit{Bifidobacterium} appeared to provide protection against maternal overweight development. In view of the microbial inoculum provided by the fetomaternal interface, along with microbe contact during delivery and through lactation, this species in particular has attracted clinical research interest [reviewed in 4].

The ultimate goal of clinical research in this context is defining an age-specific gut microbiota endorsing healthy development, documented in children remaining healthy also in the long term and thereby providing a gold standard of healthy human microbiota in the environment studied. Linking such microbiota profiles to experimental models improves our understanding of the mechanisms of host-microbe interactions in health and disease. Such research also provides microbiota markers and tools to modulate deviant microbiota development in at-risk populations. It is then the task of clinical intervention studies, in well-characterized human populations, to provide the final proof of causality for nutritional recommendations to combat the obesity epidemic.

\textbf{Disclosure Statement}

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

\textbf{References}


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