Eur J Clin Microbiol Infect Dis (2008) 27:631–634
DOI 10.1007/s10096-008-0490-x

EDITORIAL

Obesity pandemics and the modification of digestive bacterial flora

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Received: 15 January 2008 / Accepted: 7 February 2008 / Published online: 6 March 2008

Abstract Environmental factors, such as social networks, have an influence on obesity pandemics. The gut microbial flora (microbiota) plays a role in converting nutrients into calories. Variations in microbiota composition are found in obese humans and mice. The microbiota from an obese mouse confers an obese phenotype when transferred to an axenic mouse. There is a large body of experimental evidence and empirical data in the food industry showing that both antibiotics and probiotics, which modify the gut microbiota, can act as growth promoters, increasing the size and weight of animals. The current obesity pandemic may be caused, in part, by antibiotic treatments or colonization by probiotic bacteria. Using metagenomics and microarray analysis, studies of microbiota modifications after antibiotic and probiotic intake may identify the modifications associated with increased size and weight. Epidemiological studies recording these factors in an obese population may be able to link obesity with the absorption of microbiota modifiers.

Obesity is increasing among humans and is becoming a pandemic which has been rapidly developing for three decades [1]. Currently, almost 65% of the population in the USA is overweight [1]. Causes driving the obesity pandemic appear complex and a consensus is emerging to explain obesity that includes a mixture of genetic background and environmental factors. These include an increase in food availability, high-fat diet, and physical inactivity [2]; however, none of these factors can explain the constant increase in prevalence. Several types of epidemiological evidence (Table 1) show that genetics, food availability, and behavioral changes cannot easily explain the constant increase in obesity in developed countries. Recently, it was found that obesity appears to spread through social ties [3]. People in close friendships with an obese individual and the siblings and spouses of obese individuals have a higher probability of becoming obese themselves. This shows that there is a transmissibility of obesity that could be linked to a common environmental source besides genetic factors (Table 1). Therefore, the role of microbial changes in the human gut should be tested as one of the possible causes of the obesity pandemic.

Based on experimental models, it has been previously suggested that cases of obesity may be caused by an infectious agent [4]. Several viruses were associated with animal obesity. Scrapie agents were reported to induce obesity by interacting with the hypothalamic pituitary adrenal axis [4]. Recently, using a technique called metagenomics, analysis of the human gut flora by the systematic sequencing of genes in this population showed that the intestinal microbiota of obese and non-obese subjects differed (Table 1). Based on this new data and a re-evaluation of the role that human intervention plays in the weight gain of farm animals, we developed the hypothesis of a bacterial role in the obesity pandemic following the human ingestion of antibiotics and probiotics, both of which modify the gut flora.

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Table 1 Factors favoring the hypothesis of a role of the modification of the gut flora in obesity

Epidemiologic elements for a transmissible cause of obesity
- There are many examples suggesting a familial transmission (behavioral, genetic, or infectious)
- The prevalence of the disease in genetically comparable populations is widely different, depending on socioeconomic factors and the country of origin (environmental factors)
- The prevalence continues to increase rapidly in the USA in the absence of major behavioral and nutritional changes
- There is a spread of obesity in large social networks; weight gain in the human population grossly follows the level of antibiotic usage
Evidence showing a role of the intestinal microbiota in obesity
- **In humans**
- The bacterial population (microbiota) of the gut differs in obese and non-obese people
- **In experimental animals**
- The transfer of bacterial populations from obese to lean mice causes obesity
- The transfer of *Bacteroides thetaiotaomicron* + *Methanobrevibacter smithii* to axenic mice is associated with obesity and chicken inoculated with lactococcus species have increased weight/food ratio
- **In farm animals**
- Probiotics, i.e., selective strains of bacteria (mainly *lactobacillus*), used in agriculture as growth promoters are experimentally shown to aid in weight gain
- Antibiotics have been widely used as growth promoters in farm animals and have been demonstrated to help with weight gain

The role of microorganisms in the digestive metabolism

Obesity results from a disequilibrium in the energy balance, input versus output [5]. Factors determining the input are intake (food) and its conversion into energy (metabolism). The animal gut microbiota plays a major role in the digestion of nutrients. *Bacteroides thetaiotaomicron*, a common human commensal, plays a major role in converting nutrients into energy. Butyrate, a major component of the energy cycle, is produced from resistant starch dependent upon gut microbiota, specifically *Firmicutes* (Gram-positive bacteria) [6]. The digestion of starch produces hydrogen, inhibiting further digestion. Methanogenic archae, including the human commensal *Methanobrevibacter smithii*, are capable of transforming hydrogen into methane, making the fermentation provided by *Firmicutes* possible [7]. These data showed that the gut microbiota plays a major role in the digestion and energy conversion of nutrients (Fig. 1).

Human microbiota

Metagenomic sequencing of randomly amplified universal 16S ribosomal DNA was used to identify the microorganisms naturally colonizing healthy humans [8–10]. These studies showed that human microbiota outnumbered the human cells by a factor of ten, being composed of 10^{13} to 10^{14} microorganisms. The vast majority of the 72 identified species were uncultured, presumably anaerobic

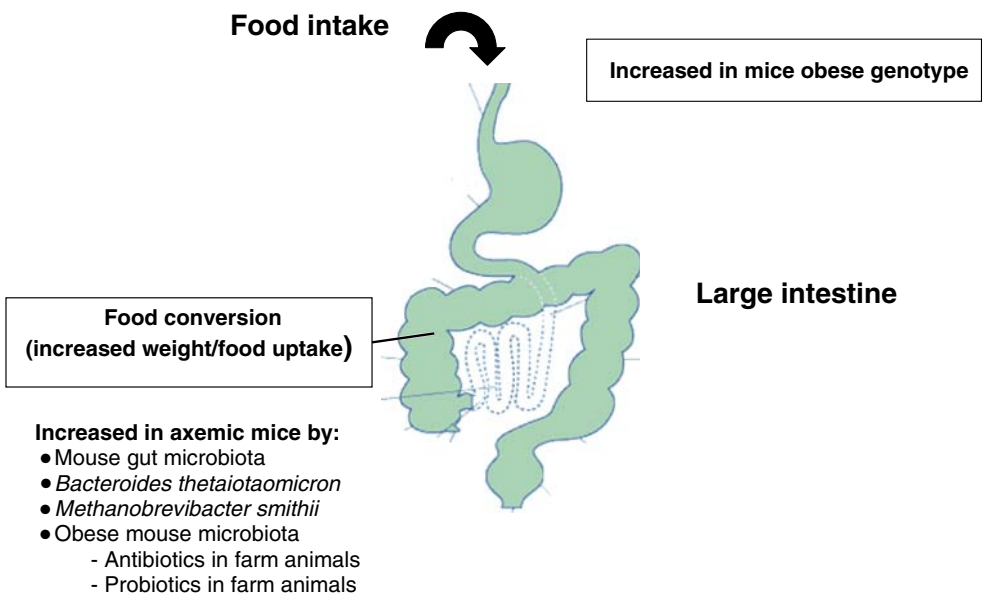

Fig. 1 The role of microbiota in increased food conversion and obesity

bacteria. They belonged to two (out of 70) bacterial divisions: the *Firmicutes* and *Bacteroidetes*. A single Archae species, *Methanobrevibacter smithii*, was found and accounted for more than 10% of the identified microorganisms.

This flora is acquired by children during the first year of life [11]. Apparently, incidental environmental exposure plays a major role in microbiota composition [11]. These studies also predicted the metabolic capability of this microbiota. The sequence of bacterial genes and the identification of their putative metabolic roles found that gut microbiota were significantly enriched in genes that encode for the metabolism of glycans, starch, various sugars, and methanogenesis. Glycans, such as plant polysaccharides, cannot be digested with human enzymes, so bacterial enzymes are needed. Finally, these studies predicted that human gut microbiota were influencing food conversion into energy.

Gut microbiota and obesity

Several studies demonstrated a role for the gut microbiota in weight gain, fat increase, and insulin resistance in mice. A team lead by JI Gordon has studied the role of gut microbiota as an environmental factor regulating fat storage [12] and playing a role in obesity [13]. The colonization of germ-free mice by mouse microbiota produces a massive increase in body fat (+60%) and insulin resistance [12]. The association of *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii* increased the metabolic activity of germ-free colonized mice [14]. Weight and fat increases in mice were not related to food consumption increase, but, rather, to food conversion ratio increases (increase of weight/ingested food weight).

They also reported variations in microbiota associated with obesity. The study evaluated the gut microbiota composition and the genetic background of mice (genetically obese or non-obese, by mutation of the leptin gene). A genetic predisposition to obesity was associated with an increase in food intake and specific obese-type microbiota. An increase of the *Firmicutes*/*Bacteroidetes* ratio was associated with the obese genotype [15]. When comparing offspring and mother microbiota in non-genetically obese mice, it was found that the offspring's microbiota reflected that of the mother. Microbiota transplantation from either lean or obese mice into the gut of germ-free mice resulted in, respectively, less or more body fat, even when the caloric intake remained the same [11]. Based on these studies, it can be concluded that the microbiota composition in mice is influenced by both genetic and environmental factors. It is linked to obesity either as a cause (transfer of microbiota) or a consequence (obese genotype).

In humans, the *Firmicutes*/*Bacteroidetes* ratio was much higher in obese than in non-obese people. Moreover, the ratio decreased when the impact of diet was also considered (either low-calorie or low-carbohydrate regimens). The authors suggested, therefore, that the microbiota may be manipulated to control weight gain [16]. Overall, these experiments show that, in mammals, an increase in body weight and fat could be associated with a modification in microbiota, even without genetically predisposing factors or increased food intake.

The role of growth promoters in agriculture: antibiotics and probiotics

The manipulation of farm animal gut microbiota by human intervention has been of major importance in the last 50 years [17]. Antibiotics promote weight gain and were among the first growth promoters used in agriculture. Probiotics can be defined as living organisms (mainly *Firmicutes*) which beneficially affect the host by improving its intestinal microbial balance. *Lactobacillus*, *Enterococcus*, and *Bifidobacterium* [17] have been widely used for this purpose in cattle, sheep, goats, pigs, poultry, horses, and pets. They modify the gut flora, specifically, the anaerobes [17]. Their role as growth promoters has been demonstrated and daily weight gain and improvement in food conversion has been shown [8]. We recently found that a single adsorption of a *Lactobacillus* strain dramatically increased food conversion and weight increase in chickens (see Fig. 2 of [18]). Taken together, the empirical data from agriculture and experimental data in laboratory animals showed that manipulating gut microbiota by antibiotic ingestion or by contamination with selected bacteria results in significant weight gain.

It is difficult to reject the hypothesis that antibiotics and probiotics may have the same effect in humans. A recent study showed that one cause of an abrupt shift in intestinal microbiota in babies was antibiotic treatment [11]. A possible link between increased antibiotic use and obesity has been proposed [19]. The role of probiotics as a source of obesity may also be evaluated. Probiotics are increasingly used in human food. Yogurts (and the milk industry in general) and other fermented foods now commonly contain *Lactobacillus* and *Bifidobacterium*. Probiotics are also used as adjuvants in many treatments for conditions ranging from diarrhea to the prevention of various intestinal diseases [20]. Their role in long-term weight gain has never been evaluated.

Conflict of interest statement None.

Support None.

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