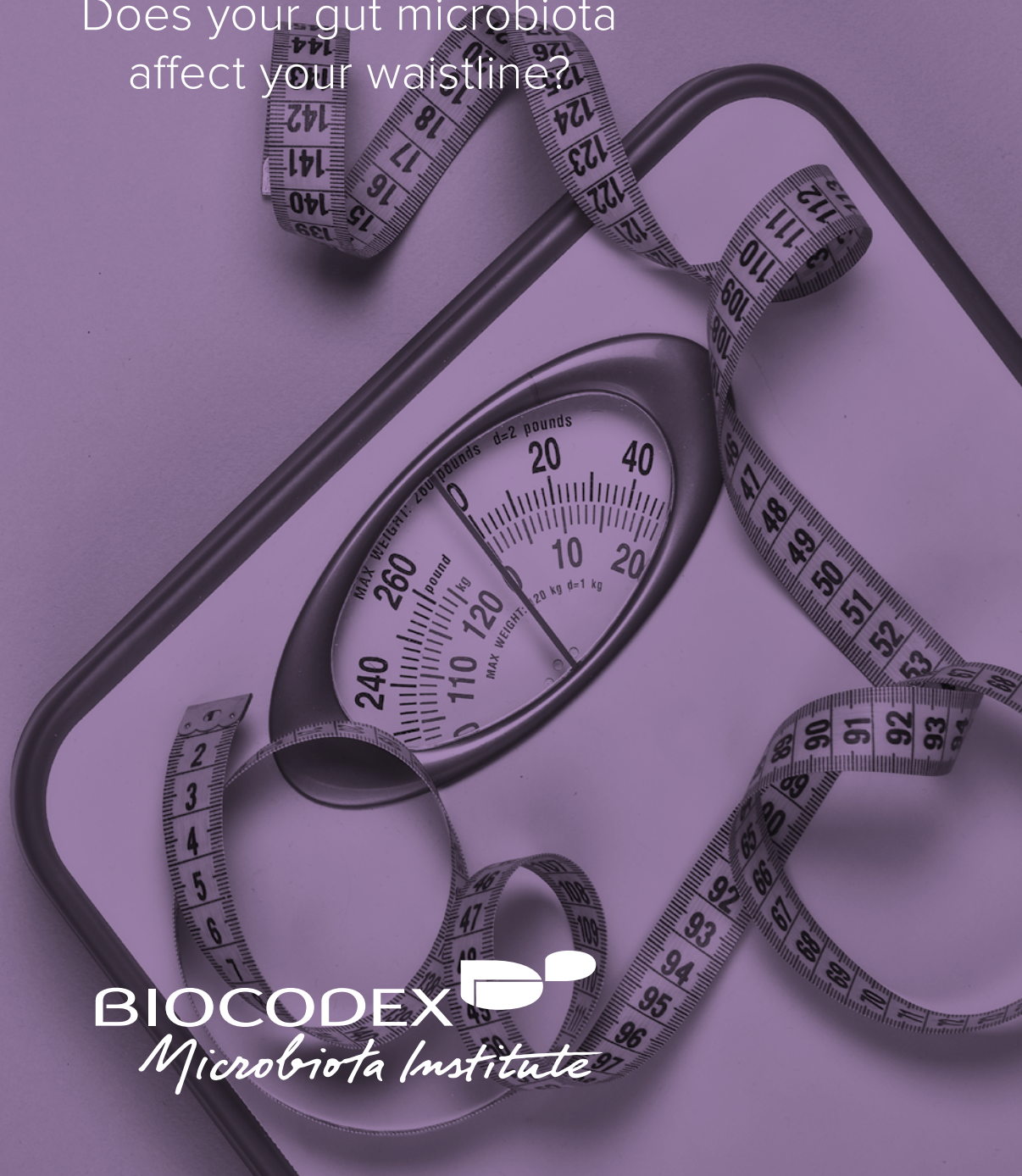
Obesity and excess weight

Does your gut microbiota affect your waistline?



BIOCODEX
Microbiota Institute

Contents

1 OBESITY AND EXCESS WEIGHT ARE SPREADING ACROSS THE GLOBE

All disease begins in the gut" **claimed Hippocrates, the father of modern medicine. And obesity seems to live up to this adage. While it is widely accepted that poor eating habits and a sedentary lifestyle are associated with this epidemic, its potential links to other factors (including gut microbiota) are currently being studied. Obesity has tripled since 1975[1], with those affected still too often accused of lacking willpower and stigmatized by societal norms. Such simplistic reasoning has probably prevented this global scourge from being taken seriously for a long time despite its serious socio-economic consequences and being the top risk factor, followed by smoking, for premature mortality attributable to an unhealthy lifestyle[1].**

KEY FIGURES[1]

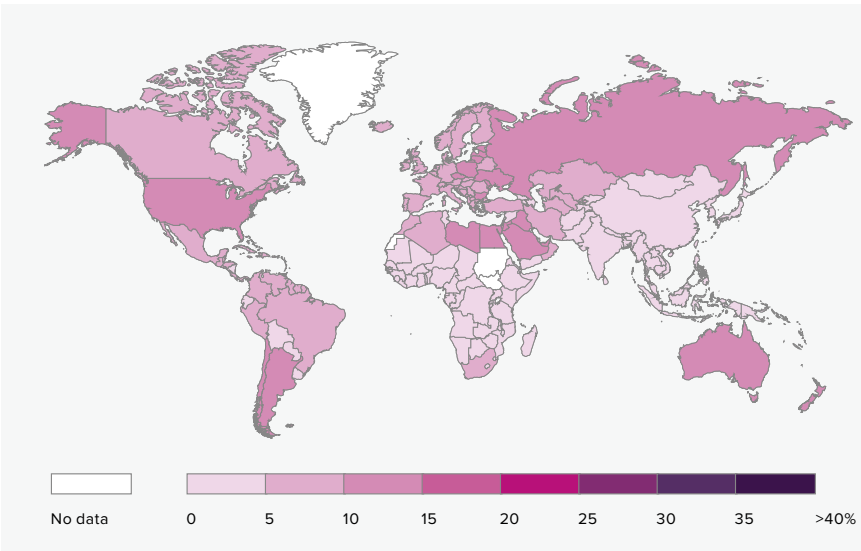
13 %
of adults in the world are obese (between 10% and 30% in Europe)

39 %
of adults are overweight (between 30% and 70% in Europe)

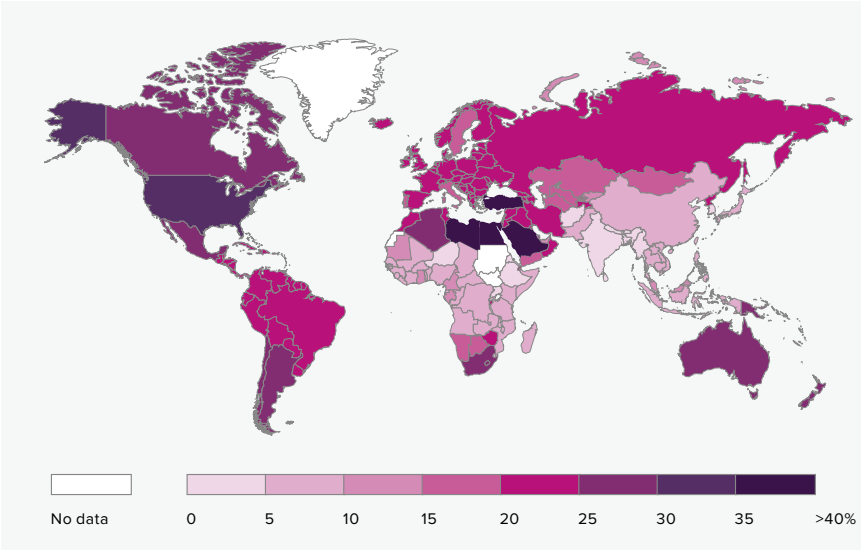
3,7 %
of adults in Japan are obese, against

38,2 %
in the United States

a PREVALENCE OF OBESITY AMONG ADULTS IN 1975



b PREVALENCE OF OBESITY AMONG ADULTS IN 2014

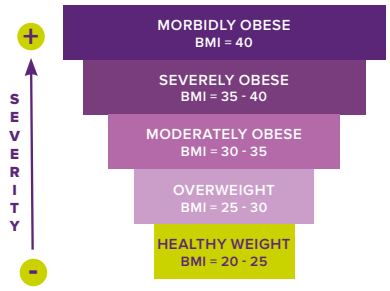


Increase in the number of obese adults over the years. Prevalence of obesity among adults by country in 1975 (a) and 2014 (b). The number of obese adults rose significantly between 1975 and 2014. Global Health Observatory (GHO) database.

1 Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-298.

HOW TO CALCULATE BMI

BMI is a person's weight in kilograms divided by the square of the person's height in meters. For example, a person whose height is 1.75 meters and who weighs at least 92 kg will have a BMI ≥ 30.04.



At a time when more people around the world die from over-eating than under-eating, obesity is defined as excessive fat accumulation in the organism[1]. It is defined by a body mass index (BMI) equal to or greater than 30. Between 1975 and 2014, the prevalence of obesity among adults increased by 7.6% in men and 8.5% in women[1]. However, such data covers up significant disparities. For example, the prevalence of obesity in Japanese adults is under 4% while the United States has ten times that number. While almost all countries are facing this pandemic (some regions of the world show particularly marked increases[2]), only Japan, North Korea and some Sub-Saharan countries still have low obesity rates[1].

A risk factor for many diseases...

The consequences of excess weight are not all apparent at first glance. But the science backs it up—people who are obese have a higher risk of developing other diseases (metabolic disorders like type 2 diabetes, cardiovascular diseases[3], depression, some types of cancer, etc.). In addition, men who are overweight have an increased risk of developing urinary disorders and erectile dysfunction, along with a drastically reduced quality of life[4]. Overall, obese people can expect to live 7 fewer years compared to those of normal weight[4].

...whose causes are not that easy to grasp

Absorbing too many calories, particularly fats and sugars, relative to actual energy expenditure is the main and now well-known cause of obesity and excess weight[1,5]. Yet sometimes adopting healthy behaviors (good nutrition, physical activity, etc.) is not enough to reabsorb the excess weight[1]. What are the hidden causes?

Heredity

First off, genetic factors: programmed to withstand hard times (famine for example), human beings inherited genes that enhance their ability to store calories[1]. Studies on mice and humans even suggest that obesity (including its most severe forms) could be hereditary in 40% to 70% of cases[1]. However, obesity-associated genes cannot alone explain the current epidemic.

"Obesogenic" environment

Genes can also be influenced by the environment. As it profoundly affects our behaviors, the environment certainly plays an important role in determining an individual's build. The increase in the obesity rate over the past 50 years has coincided with changes in our lifestyle, including extremely high levels of fat, sugar and salt in processed foods; increased consumption of fast food and snacks; altered work-life balance; lack of physical activity; lack of sleep or reduced quality of sleep; social stress, etc [1]. Daily routines that over time could have caused changes to genes that are passed down and predisposed future generations to an increased risk of obesity: such mysteries are referred to as "epigenetics"[1]...

Gut-brain miscommunication

The gut, at last. As the body's true "second brain", it communicates with our gray matter via an axis that monitors metabolism, i.e. the balance between energy intake and energy expenditure[6]. When it malfunctions as in obese people, it becomes unable to regulate appetite, satiety and energy storage[7,8]. Studies confirm that when mice are deprived of gut microbiota and subjected to a high-fat diet, they do not gain weight. In contrast, in animals with intestinal flora, the same diet leads to weight gain[7]. More surprisingly, if a lean mouse receives a microbiota transplant from an obese subject, it will in turn gain weight. Cause or consequence? For now, researchers are struggling to find answers and identify the underlying mechanisms[5,8].

2 Bangladesh, Bhutan, India, Nepal and Pakistan, Indonesia, Philippines, Malaysia, Vietnam, Thailand, Sri Lanka, Belize, Cuba, Dominican Republic, Puerto Rico, Argentina, Brazil, Chili, Paraguay, Uruguay

3 Abenavoli L et al. Gut Microbiota and Obesity: A Role for Probiotics. Nutrients. 2019 Nov 7;11(11). pii: E2690.
4 Barathikannan K et al. Gut Microbiome Modulation Based on Probiotic Application for Anti-Obesity: A Review on Efficacy and Validation. *Microorganisms*. 2019 Oct 16;7(10). pii: E456.
5 Maruvada P et al. The Human Microbiome and Obesity: Moving beyond Associations. *Cell Host Microbe*. 2017 Nov 8;22(5):589-599.
6 Cerdó T et al. The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity. Nutrients. 2019 Mar 15;11(3). pii: E635.
7 Lee Clare J et al. Gut microbiome and its role in obesity and insulin resistance. *Ann N Y Acad Sci*. 2020;1461(1):37-52.
8 Torres-Fuentes C et al. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol. 2017 Oct;2(10):747-756.

2. GUT MICROBIOTA AND OBESITY: A CHICKEN AND EGG SITUATION

The 100 trillion microorganisms (bacteria, viruses and fungi) that live in the gastrointestinal tract are actively involved in our body's ability to properly absorb nutrients. However, eating a diet high in sugar and fat results in a disturbed energy balance. Disrupted in turn (less rich and diverse), the gut microbial ecosystem is no longer able to regulate the excess energy absorbed and itself contributes to maintaining this imbalance.

Is there a link between gut microbiota and weight?

The gastrointestinal tract is populated by bacteria, viruses and fungi. Among them, the two dominant bacterial phyla (Bacteroidetes and Firmicutes, including lactobacilli) represent nearly 90% of the gut microbiota[3]. The remaining 10% consists of Proteobacteria (including *Escherichia coli*, known to be sometimes harmful) and Actinobacteria, including beneficial bifidobacteria[3]. A well-balanced gut microbiota contributes to good health and a number of processes. It aids digestion and proper intestinal cell function, interacts with the immune system, prevents invading molecules and bacteria from crossing the gut epithelium and also communicates with the brain. In obese and overweight individuals, the gut microbiota seems to be unbalanced (dysbiosis). This means it is generally less abundant and diverse[9] with a reduction of beneficial bacterial species such as *Akkermansia muciniphila* and bifidobacteria and an increase in potentially harmful bacteria that contribute to weight gain through yet-to-be-understood mechanisms.

The vicious cycle of dysbiosis

Be it the cause or the consequence, gut microbiota plays a role in obesity. When altered, there are many health implications including digestive disorders, impaired defense mechanisms and its reduced capacity to communicate with the brain to control hunger[8]. These disturbances in turn maintain gut microbiota dysbiosis[9]. More than just a metabolic disorder, obesity would therefore be associated with brain and immune system dysfunction which manifests itself in abnormal eating behaviors in which gut microbiota plays a role[3,4,8,10].

Let us explain!

9 Mulders RJ et al. Microbiota in obesity: interactions with enteroendocrine, immune and central nervous systems. *Obes Rev.* 2018 Apr;19(4):435-451
10 Rastelli M et al. Gut Microbes and Health: A Focus on the Mechanisms Linking Microbes, Obesity, and Related Disorders. *Obesity (Silver Spring).* 2018 May;26(5):792-800.

Obesity and excess weight

THE COMPLEX RELATIONSHIP BETWEEN A PERSON AND ITS GUT MICROBIOTA

Digestion and metabolism

BALANCED MICROBIOTA

- Facilitates the digestion of lipids and their absorption by the intestines[4,7]
- Contributes to increased energy expenditure and the balance between calorie intake and output [4,7]
- Helps to assimilate indigestible foods (fibers) and convert them into sources of energy for the body, referred to as short-chain fatty acids (or SCFAs)[6,7]

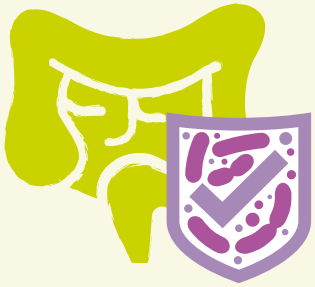
DISRUPTED MICROBIOTA

- Alters the regulation of fat storage[6]
- Contributes to excessive energy extraction from food consumed[3,7,9]
- Disrupts the ability to balance blood sugar levels[6]

Gut barrier and immunity

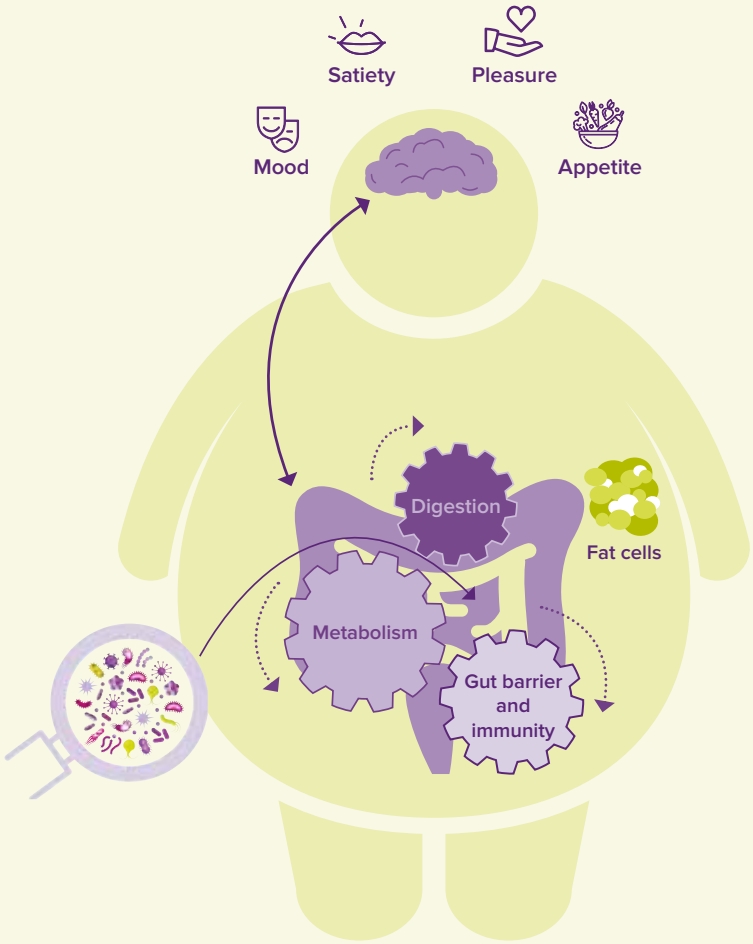
BALANCED MICROBIOTA

- Enhances the integrity and proper functioning of the gut barrier[9]
- Prevents the passage of harmful bacteria from the intestines into the bloodstream[9]



DISRUPTED MICROBIOTA

- Alters the integrity of the gut barrier[9]
- Allows the passage of harmful bacteria from the intestines into the bloodstream[6,10]
- Causes the immune system to trigger an inflammatory response to protect the body[9,10]
- Contributes to maintaining persistent, low-grade inflammation[9,10]
- Sets off a cascade of events leading to an increase in blood sugar levels, liver fat levels and weight gain[3,6,7,10]...



Gut-brain axis

BALANCED MICROBIOTA

- Facilitates communication between the gut and brain especially *via* signaling molecules (including SCFAs and neurotransmitters)[3,4,10]
- Helps the brain regulate energy balance, appetite and the feeling of satiety[3]
- Modulates mood and eating behavior by activating the brain's reward and pleasure circuits[8,10]
- Analyses messages from the brain and, in turn, makes any necessary adjustments[8,9,10]

DISRUPTED MICROBIOTA

- Alters communication between the gut and brain[8,9,1]
- Disrupts messages sent to the brain's reward circuit, creating a pleasure deficit[8,9,10]
- Contributes to a reduced feeling of satiety[8,9,10]
- Plays a role in stimulating appetite[8,9,10]

SCFAs: short-chain fatty acids, a source of energy (fuel) for the body

Neurotransmitters: specific molecules that enable communication not only between neurons but also between neurons and microbiota bacteria

3. MODULATING THE GUT MICROBIOTA: EFFECTIVE FOR LOSING WEIGHT?

Melting excess pounds away by balancing the microbiota—is hope within reach? Perhaps, at least as long there is a better understanding of how food, probiotics, prebiotics and fecal microbiota transplant (FMT) impact the gut microbial ecosystem. While the war on obesity is not yet won, it has most certainly been declared!

Urgent need to reassess eating habits

Diet is both the leading risk factor for obesity and the main lever in gut microbiota modulation. Unsurprisingly, the composition of the gut is shaped by dietary preferences. For example, omnivores have a higher diversity of bacteria compared to vegetarians. Similarly, microbiota is dominated by certain specific species in consumers of animal fat and protein, etc[3]. In theory, it seems easy to "remedy"... Wrong! Responses vary from person to person. Despite a great number of studies, no direct link has currently been established between action on the flora and the amount of weight loss[11]. Some researchers believe that initial composition of our gut microbiota explains the variability in responses to diet[7,11] while others feel that it is even a good predictor of success[7]. Among this controversy, only one thing is certain—healthy eating matters, even if some of us gain weight more easily than others!

Bariatric surgery

Among the treatments available to morbidly obese patients, bariatric surgery is one of the most effective. It consists in reducing the size of the stomach or bypassing all or part of the small intestine. In addition to weight loss, the procedure affects gut microbiota[7,9]. Researchers even believe that the alteration of microbiota following surgery is directly responsible for the decline in fat mass and the host's reduced ability to use food as fuel[9].

11 Seganfredo FB et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. Obes Rev. 2017 Aug;18(8):832-851.

Probiotics, a promising solution?

Probiotics are “live microorganisms (bacteria, yeasts) that, upon ingestion in sufficient concentrations, can exert health benefits to the host”[12,13]. These microorganisms are found in fermented foods (yogurt, kefir, sauerkraut, etc.), or in the form of probiotic drugs or dietary supplements. Their ability to restore the microbiota balance makes them a promising tool in the fight against obesity[3]. To study their effect on weight loss, the body’s ability to regulate blood sugar levels despite a fatty diet, the feeling of satiety, the drop in the body mass index (BMI), the decline in fat mass, etc., laboratory mice were examined from every angle after being fed probiotics[3,4,6,14,15]. One of the results was that some lactobacilli, bifidobacteria, other bacteria with complicated names (*Akkermansia*, *Hafnia*, *Pediococcus*, *Bacteroides,*etc.) as well as a yeast, came out on top. Mice treated with these probiotics showed an improved metabolic profile and reduced weight gain[6,14,15]. One of them even had a promising appetite-suppressant effect and contributed to the feeling of satiety. There is less data on humans, and only some specific probiotics had an impact on weight, BMI, waist circumference, fat mass and metabolic profile[3,4,6]. Despite these encouraging results, more research is needed to find out whether humans respond in the same way[3,6].

12 Food and Agricultural Organization of the United Nations and World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. (2001). http://www.fao.org/3/a-a0512e.pdf

13 Hill C et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506-514.

14 Lucas N et al. Hafnia alvei HA4597 Strain Reduces Food Intake and Body Weight Gain and Improves Body Composition, Glucose, and Lipid Metabolism in a Mouse Model of Hyperphagic Obesity. Microorganisms. 2019;8(1):35.

15 Legrand R et al. et al. Commensal Hafnia alvei strain reduces food intake and fat mass in obese mice-a new potential probiotic for appetite and body weight management. Int J Obes (Lond). 2020;44(5):1041-1051.w

What about prebiotics?

It's the same story for prebiotics. These non-digestible sugars—present in vegetables, whole-grain cereals, legumes, tubers, fruits, nuts, herbs, spices, etc.—nourish good bacteria allowing them to proliferate to the detriment of bad bacteria. While their benefits in combating obesity have been widely demonstrated in the laboratory, human studies have produced divergent results[6]. Some prebiotics induced a significant reduction in weight, BMI and waist circumference in obese and overweight adults, while others had no effect[6]. As a whole, studies show that prebiotics affect satiety[7], but unfortunately this does not lead to weight loss[6]. Although prebiotics remains an exciting line of research, experts agree that it is still too early to recommend their use in treating obesity and excess weight[6].

An unusual transplant!

Fecal microbiota transplant (FMT), also known as stool transplant, is another method which may well prove promising[16]. Currently prescribed to treat a sole condition far removed from obesity (recurrent *Clostridium difficile* infections), the procedure consists in this case in transferring microorganisms contained in the stool of donors with normal BMI to obese recipients to "correct" their flora[17]. Several research teams are currently exploring the potential value of this approach. They are thoroughly examining its effect on gut microbiota restoration, eating behavior and the proper use of energy resources based on calories consumed[17].

16 Lee P et al. Gut microbiota and obesity: An opportunity to alter obesity through faecal microbiota transplant (FMT). Diabetes Obes Metab. 2019;21(3):479-490.

17 Live microorganisms (bacteria, yeasts) that, upon ingestion in sufficient concentrations, can exert health benefits to the host. They are found in fermented foods (yogurt, kefir, sauerkraut, etc.), or in the form of probiotic drugs or dietary supplements.

While the study of gut microbiota opens up new ways to treat obesity, one must proceed with caution. This approach is "just one treatment among others", explains Prof. Patrice D. Cani, co-director of the Metabolism and Nutrition research lab at Louvain Drug Research Institute of the Catholic University of Louvain (UCLouvain, Brussels, Belgium).

Are we destined to keep our extra pounds?

Broadly speaking, belief in a miracle cure is delusional. No treatment can beat obesity without the active participation of the subjects (diet, exercise, etc.) and an integrated and personalized approach to their care. Obesity is a long-term complex condition that depends on multiple related factors, including gut microbiota. However, to claim that an imbalance in the microbial ecosystem inevitably leads to obesity (or conversely that a balanced one ensures a normal weight) is a mistake. It is nonetheless a good idea to maintain a balanced gut microbiota, which is part of a comprehensive and personalized treatment for patients.

> **“ MY MOTTO IS « IN GUT WE TRUST ». ”**

Is it risky to act on microbiota on one's own?

From a strictly medical standpoint, the approach is relatively safe, provided that consumers choose a probiotic[17] whose advanced effects are based on scientific proof and whose bacterial composition is known (Lactobacilli and Bifidobacteria for example). It is a myth to think that all probiotics are the same as the specific bacterial strain used plays a critical role in their action. Lastly, the consumption of prebiotics[18] should also be encouraged. However, new users should particularly avoid taking excessively high doses as they might experience unpleasant side effects such as bloating, diarrhea, abdominal pain, etc. If truth be told, the greatest risk is a psychological one—namely being disappointed if promises are broken!

Has gut microbiota transplant been oversold?

Many studies are currently underway on the topic. Some of them show that transplanting microbiota would have no effect on obesity or that it would result in a temporarily improved ability to stabilize blood sugar levels. Results have been disappointing, but provided much valuable information. We now know that donor and recipient microbiota must be compatible. We have also learned that some individuals are more receptive than others to transplant (the same goes for dietary changes) depending on the initial composition of their microbiota. In any event, improving our health by focusing on gut microbiota is a promising avenue, as long as we act reasonably and follow medical and dietary recommendations. Personally, I am convinced of it as my motto is "In Gut We Trust".

18 Sugar which serves as food to good bacteria. It can be found in bananas, leeks, onions, artichokes, etc.

Obesity and excess weight

DOES YOUR GUT MICROBIOTA AFFECT YOUR WAISTLINE?

The global scourge of obesity has skyrocketed in just 30 short years. No region of the world has now been spared, with more people dying from eating too much than from not eating enough.

Too much fat, too much sugar, not enough exercise... The disease is still too often associated with an unhealthy diet and a sedentary lifestyle. But other less-well-known factors could also play a role, such as heredity, daily living environment and especially miscommunication between gut and brain.

In concert with our gray matter, the large number of microorganisms living in our gut may thus be affecting our eating behaviors (appetite, feeling of satiety, mood, reward pathway, etc.), our metabolism (fat storage, blood sugar levels), our immune response (chronic inflammation) and the integrity of our gut barrier.

While watching what you eat is indispensable no matter what approach you take, bariatric surgery has shown positive results in those suffering from the most severe forms of the disease. However, the arsenal that is now available may well be moving towards a personalized approach and could include, in the future, actions on gut microbiota.

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