THE OBESE CYCLE:

FROM MOTHER TO CHILD TROUGH THE GUT MICROBIOME

Tatjana Pchenitchnikova
S 1899643
June 2016
Jinyuan Fu & Alexandra Zhernakova
UMCG, Departement of Genetics
University of Groningen

university of groningen

umcg

The relationship between the gut microbiome and human disease are recognized a long time ago [1]

‘‘All diseases begin in the gut.’’

Hippocrates (460–370 B.C.)

SUMMARY

Obesity is one of the largest public health problems nowadays. This is the reason why we want to understand the source of obesity. It is already known that children of obese parents have a predisposition to develop obesity, even despite the fact that this is not fully explained by genetics. As there is a vertical transmission of the gut microbiome from mother to child, the obese microbiome is transferred to the infant during birth, resulting in an obese cycle. This obese-cycle will be investigated in this review, because it gives more insight into the role of the microbiome in relationship to obesity.

When obese the microbiome shows a decreased number in Bifidobacteria and Bacteroidetes, an increased number Firmicutes and Proteobacteria and a lower diversity. In addition, pregnancy also causes alterations in the microbiome of the obese woman. These alterations lead to several alterations in the maternal body such as decreased insulin sensitivity, increased body fat promoting pro-inflammatory cytokines, increased energy harvesting and alterations in satiety metabolites and hormones. The obese bacteria are also seen in the early microbiomes of infants who were obese later in life. The way of delivery and breast feeding are a part of the vertical transmission of the microbiome, whereas the use of antibiotics or pre- and probiotics are not a part of the transmission, but play a critical role in the development of the microbiome during the first 12 months.

Thus, the infant has an obese microbiome and influences from the mother's obese microbiome. This will drive the infant to obesity, therefore continuing the obese cycle by passing the obese microbiome through to their offspring.

INDEX

INTRODUCTION

Since obesity is one of the most common public health problems in the modern world, it is an important topic to investigate in relationship to the gut microbiome, especially due to the association with many "first world diseases", such as insulin resistance, type II diabetes mellitus, hepatic steatosis and steatohepatitis, dyslipidemia and atherosclerotic cardiovascular disease [2].

More recently, research into the gut microbiota has become one of the most studied factors in relationship to diseases [3]. Due to recent advances in sequencing technologies, the wider use of metagenomic analysis for studying complex ecosystems such as the human gut has become possible [4]. The most used techniques to analyze the composition of the gut microbiome are to sequence the feacal sample using 16S rRNA sequencing and shotgun sequencing (metagenomics). After that the metagenomic sequence reads are assembled by using bio-infomatical approaches and the big data is processed into understandable information [Fig.1[5]] [2,6]. An important advantage of this metagenome analysis is that it identifies genomes of bacteria which are not possible or rather hard to culture in vivo. The metagenomic sequences can also be used for quantitatively accurate estimation of the bacterial composition by mapping the reads to reference genomes of human microbes [6].

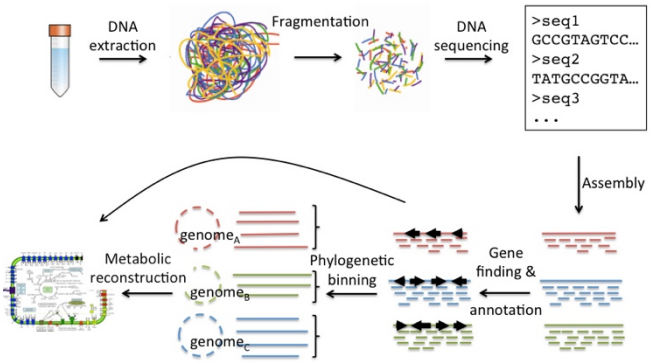

Fig. 1 - The steps in the process to determine the composition of the gut microbiome from a single sample. Using the 16S rRNA and metagenomics for the study of the human gut microbiome.

Due to the research that was done in the last years on the human microbiome, we discovered that the human gut microbiota contains more than a 100 trillion commensal bacteria, distributed over more than 1000 different species [6,7]. However, each person has a distinct and unique microbiome, a conserved set of gut bacteria are shared among individuals. Firmicutes and Bacteroidetes dominate 90% of the gut's microbiome in healthy people [6].

It is already known that children of obese parents have a predisposition to develop obesity. There are many studies investigating the inheritance of obesity; however, it is clear that it could not be fully explained by genetics [8]. Since gut microbes can be transferred from mother to infant during birth, an obesity-associated microbiome may be transferred from an obese pregnant woman to her offspring [3]. Other studies revealed that the first days and weeks of the infant is a crucial period for the programming of the gut microbiome. This programming contributes to functions such as energy harvesting, shaping the host immune system, metabolism of xenobiotics and metabolic signaling. If this programming is not correct, it leads to alterations which are unhealthy [1,6,9].

The inheritance of an obese microbiome from the mother during labour and first year of life may be the key factor in becoming obese later in life – a continuous cycle of obesity across generations. This obese-cycle, and some of the co-factors, are important to investigate, because it gives more insight into the role of the microbiome in relationship to obesity and provides information on how to disrupt this obese cycle. The aim of this review is to give an

insight in the transmission of the obese microbiome from mother to child and look at some of the critical co-factors which can alter the infant's microbiome.

This review will start with an explanation of the obese microbiome, the influence of the pregnancy and the alteration in pathways due to the dysbiosis. After this we will discus how the microbiome is transferred to the infant and some of the co-factors which affect the infant's microbiome, and ending with the clinical outcomes for the infant. The structure of the thesis is shown in the figure [Fig. 2] below.

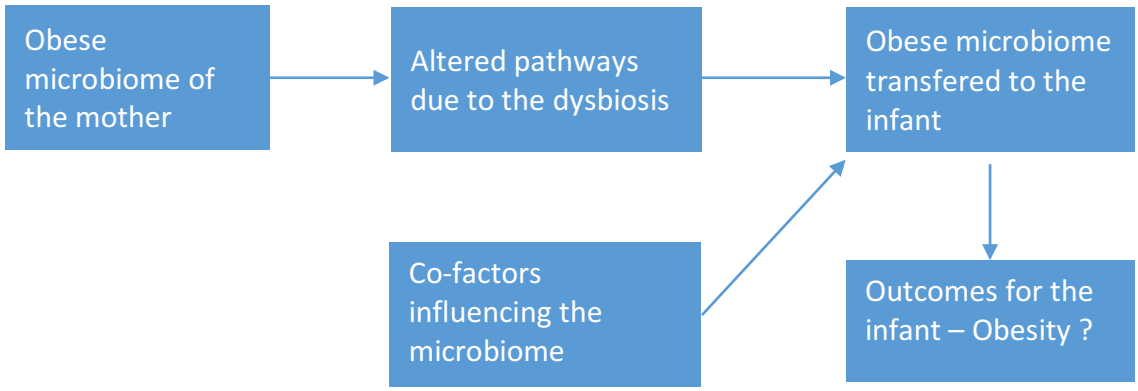

Figure 2 – The obese cycle

1 The obese microbiome

As mentioned in the introduction, the human microbiome consists of billions of bacteria. Different animal and human studies demonstrate that the human gut microbial communities differ between obese and lean phenotypes. Here we will discuss the obese microbiome and the influence of pregnancy on the microbiome.

1.1 Obese gut microbiome

One of the most contributing factors to obesity is the Western diet, which is full of high simple carbohydrates, fats, and animal proteins, is linked to an imbalance of the gut microbiome [10]. Many studies demonstrated that the microbiome of obese people showed decreased levels in Bifidobacteria and Bacteroidetes and an increased number Firmicutes [1,2,3,6,9, 11]. Other studies showed an increase in Clostridium innocuum, Eubacterium dolichum, Catenibacterium mitsuokai, Enterococcus species, Staphylococcus, Enterobacteriaceae and Escherichia coli [11, 12]. In studies where high-fat diets were examined, the participants had a reduced number of Bacteroidetes, and increased numbers of Firmicutes and Proteobacteria [2,7]. The abnormal high energy intake seen in obese people is linked to the increased microbes and a lower microbial diversity, compared to lean people [2,4,7]. The main findings of the aforementioned studies in terms of increase and decrease are summarized in Table 1.

Author	**Findings in obese people**
Holmes et al. [1]	Firmicutes:Bacteriodite ratio ↑
Tschop et al. [2]	Bacteriodites ↓ Firmucutes, Actinobacteria ↑
Gohir et al. [3]	Proteobacteria, Actinobacteria ↑ Bacteriodites, Staphylococcus ↑ Bifidobacterium, Bacteriodites ↓
Fukuda and Ohno [6]	Clostridium, Bifidobacteruim ↓ Lactobacilli/Entrococci, Bacteriodites ≈
Houghteling and Walker [9]	Bifidobaceria ↓ Staphylococcus ↑ Firmicutes:Bacteriodite ratio ↑
Garcia-Mantrana and Collado [11]	Firmicutes:Bacteriodite ratio ↑ Microbial diversity ↓

Table 1 – The main findings of the aforementioned studies, where obese and lean people are compared to each other. The findings show the difference in obese people.
↑ - increased ↓ - decreased ≈ - no difference

This review explains the transmission of the obese microbiome, thus the obese mother needs to be pregnant to have the ability to pass the microbiome to the infant. Therefore it is important to investigate if the pregnancy has an influence on the microbiome. This issue will be discussed in the following section.

1.2 Influence of pregnancy

Not only does the gut microbiome differ between obese and non-obese individuals, but also the maternal microbiome undergoes some changes throughout the pregnancy. The maternal gut microbiota differs between women with normal weight and women with obesity

particularly in the second half of the pregnancy. Obese women have increases in the Firmicutes phylum (*Staphylococcus*) as well as increases in some Proteobacteria (*Escherichia coli)* [13]. Overweight pregnant women have an increase in Staphylococcus, Enterobacteriaceae and Escherichia coli and a decrease in Bifidobacterium and Bacteroides [1,3]. This altogether results in an unhealthier microbiome in the mother's gut.

Now, the question arises if the changes in the microbiome are spread evenly throughout the whole pregnancy. The short answer is: no. From the first trimester to the third trimester, the relative abundances of Proteobacteria increased in 69.5% of the women and the Actinobacteria and Faecalibacterium prausnitzii were increased in 57% of the women [14,15]. In addition, the weightgain during the pregnancy positively associated with the abundance of Bacteroides and inversely associated with the abundance of Bifidobacteria. The counts of Bacteroides and Staphylococcus aureus are also higher in the third trimester [3]. The α-diversity was richer and had a more even taxonomy distribution in the first trimester, compared to the third. This suggests a relative overall abundance of the α-diversity toward the end of the pregnancy [11,15]. In the first trimester bacteria witch are correlated with butyrate producing bacteria such as Faecsibacterium and Eubacterium were overrepresented. On the other hand, the Streptococcus genus and the Enterobacteriaceae family were overrepresented in the third trimester. There are also indications that there is an increase in Proteobacteria and Actinobacteria the end of pregnancy. Proteobacteria are known as a harmful bacteria and found in the gut of people with metabolic diseases and inflammation. On the other hand, the Actinobacteria, contains one of the most beneficial bacteria in the phylum, the Bifidobacteria [3,11].

These findings show alterations in the microbiome of obese mothers during pregnancy. This shift is quite surprising because one would expect the maternal microbiome be as healthy as possible for the fetus. On the other hand, in a pregnant state the maternal body should be prepared to provide an environment for the fetus where the fetus can grow and develop.

To summarize this section: the characteristics of an obese microbiome are decreased levels in Bifidobacteria and Bacteroidetes, an increased number Firmicutes and a lower bacterial diversity. Furthermore, the pregnancy itself also alters the mother's microbiome. All together it shows that the microbiome of an obese and pregnant woman is changed compared to a normal state, leading to alterations in the downstream pathways.

2 Impact of the maternal dysbiosis

Due to the commensal relationship between the body and the gut's microbiome, it is logical that with an altered microbiome there are alterations in some of the maternal pathways. The alteration in the obese microbiome and pregnancy are leading to alteration in the immune system, metabolism and hormones of the mother. This is the second step in the obese cycle (Fig.2). We will show that this step is crucial in keeping the obese phenotype.

2.1 Insulin sensitivity

One of the altered pathways is the insulin sensitivity. Secretion and sensitivity of insulin are changed in order to provide more glucose to the fetus. In the second trimester of the pregnancy, the insulin sensitivity is reduced by 50-70% as compared to a non-pregnant state. In the third trimester, there is a decline or even a cessation of fat accumulation, coinciding with an increase in adipose tissue lipolysis in association with the increase in insulin resistance[1,2,4,19]. When obese, the mother is already associated with increased insulin resistance [3,6,9, 16] and hyperlipidemia. The last one correlates with high birth weight and with increased infant body fat [9,16]. Increase in butyrate-producing bacteria has a positive relationship with a decrease in insulin sensitivity [6]. These finding conclude that not only obesity, but also pregnancy is related to an increased insulin sensitivity.

2.2 Increased energy harvesting

Not only insulin sensitivity is altered in obese people, the energy harvesting is altered in these people. The microbiome associated with obesity is more efficient at harvesting dietary energy, than the microbiome of a lean person [2,3]. Studies have reported that the energy harvesting is increased in obese people due to the changes in the bacterial composition. The increased energy harvesting leads to an increased body weight.

Koren et al. measured a significant increase in stool energy content between trimesters within individual women (4.4 ± 0.6 versus 4.7 ± 0.6 Kcal/gram dry weight [gdw]; $p = 0.002$). This difference in energy is already correlated in murine studies to the host adiposity and for the altered microbiomes which are associated with high nutrition load. Although in these cases the difference in energy is not related to high nutrition load because the woman does not increase their levels of food intake, but it can be related to the shift in microbiome from first to the third trimester. To find out whether this extra harvested energy is correlated to an enrichment of specific metabolic pathways and the microbiome composition, the authors [14] preformed a shotgun metagenomic analysis of first and third trimester samples. The analysis did not show any differences in the mean relative abundance in metabolic pathways [14]. This is also supported by the study of Kolva et al. They reported that energy harvest of ~150 kcal, due to an altered intake, was associated with an increase in gut microbial abundance of Firmicutes and a reduction in Bacteroidetes [4, 17]. Therefore, the extra energy that is harvested can lead to an overweight phenotype in the gut.

Another study reports that the placental transport also depends on the concentration of nutrients in the maternal blood. A higher concentration gradient leads to increased diffusion and therefore increased fetal and placental growth. An obese pregnancy where the nutrient availability is increased, may also affect placental growth directly [16]. This can affect the fetus by increasing the risk of being overweight, not even born yet.

These results in an increase in energy for the mother, keeping her obese if she does not take changes in het lifestyle. Due to the increased nutrition availability the availability of the nutrition's is increased for the fetus, what stimulates the growth of the fetus and thereby the risk of being obese.

2.3 Inflammatory levels

Another altered pathway is the immune system. The microbiome plays an important role in the shaping of the immune system. Therefore, alterations in the microbiome during pregnancy or obesity alter the immune system of the host.

As mentioned before, the level of Proteobacteria in the third trimester is higher. These bacteria are associated with an increased level of inflammation [14]. The levels of the pro-inflammatory cytokines IFN-γ, IL-2, IL-6 and TNF-α were significantly higher during the third trimester [2,7,9]. These findings are also confirmed with germ-free wild type mouse [4,9]. This is quite interesting because a pregnancy usually is associated with an anti-inflammatory condition due to the placental interference. The adipose tissue also secretes inflammatory cytokines such TNF-α, IL-6 and plasminogen activator inhibitor type 1. In addition, the placentas from obese pregnant woman have higher mRNA transcript abundance of a number of inflammatory markers, like IL-1b, IL-8 and MCP-1[17]. These higher mRNA transcripts contribute to a pro-inflammatory environment in the placenta.

The increase in gram-negative bacteria, relates to an increase in bacterial liposacharides (a component of the Gram-negative bacteria's cell wall). The translocation from the intestinal lumen to the circulation, induces inflammation through the activation of the toll-like receptors on the macrophages and the intestinal epithelial cells. Contributing to the pro-inflammation condition in the gut [10].

Summarizing, the pregnant mothers with obesity have increased levels of pro-inflammatory cytokines in their system which leads to an unhealthy environment for the fetus or infant.

2.4 Short chain fatty acids (SCFA)

The last pathway discussed is related to the short chain fatty acids. Bacteriodites and Firmicutes secrete short chain fatty acids by the anaerobic fermentation of dietary fiber. These SCFA's can act as a regulator of the host metabolism and immune system leading to a pro-inflammatory environment in the gut and increasing the energy consumption.

Intestinal bacteria and their SCFA metabolites can influence gut satiety hormone levels that regulates the appetite and the sense of fullness [7,8]. Leptin and adiponectin, other satiety hormones, is secreted by adipose tissue [16]. Another study by Garcia-Mantrana mentioned the study of Khodabakhshi where the different types op satiety hormones, such as leptin, ghrelin and adiponectin were studied. They found a significant higher levels of ghrelin in the milk of mothers with lean children, compared to mothers with obese children [11]. This means that the mother can pass the ghrelin to their infant and thereby may protect the child from being obese.

Another function of SCFA is to act as important microbial signals to remodel the gut's microbiome activation of the inflammasome, thereby helping to prevent chronic inflammatory

responses to microbes and their products. They also up regulate the regulatory T-cells in the gut and bend the lamina propria macrophages into a hypo-responsive state in relationship to normal gut microbes by down regulating the pro-inflammatory signals. These pathways help to shift the cells toward an anti-inflammatory phenotype [7] which plays an important role in the infants gut.

To reiterate all above: alterations in the gut microbiome alters the production in SCFA's. As mentioned earlier, the obese microbiome shows a decrease in the Bacteriodites what means that the production of the SCFA is decreased, shifting the metabolic alterations in a more obese phenotype.

3 Transmission of the microbiome to the child

The alteration in the mother's microbiome can be passed to the infant during labour. Several studies demonstrate that infants born to obese mothers have a different bacterial colonization pattern than those born to lean mothers. These differences are not short-term but are maintained during the first years of life. The vertical transmission of the microbiome is the most important way for the colonization of the infant's microbiome, even though it is not the only way for the infant to obtain the bacteria for the microbiome.

3.1 Before birth

The infants gut seems to be free of bacteria before birth; therefore, the gut should be colonized somehow to obtain a microbiome. The maternal vaginal and gut bacteria are the vertical transmission of the microbiome to the child. However, there is a suggestion that the uterus is not sterile and microbial exposure may begin in utero. Consequently, this would be the first colonization of the infant's microbiome [1,2,10,12]. Despite the fact that there are some studies suggesting this, there should clearly be more research into this field to obtain significant results.

3.2 Way of birth

When born in the natural way, the infant gut is initially colonized with Proteobacteria and Firmicutes, followed by a gradual increase in Actinobacteria (potentially due to the introduction of breast milk) [18]. The gut microbiota of the infant at the age of 4 days is mostly dominated by Gammaproteobacteria and some Staphylococcus species, followed by subsequent Bifidobacterium and Bacteroidetes colonization [2,7,9,19]. Leading to a healthy microbiome and correct programming of the microbiome. Despite of this it, obese woman have different concentrations of bacteria and the infant is colonized with obese bacteria.

A review of the early infant microbiome and childhood obesity reported that despite a global reduction of the Bacteroidetes and Bifidobacterium [2,12,17], increase in the Bacteroides fragilis, Lactobacillus [1,2] and Staphylococcus aureus in the first six months is correlated with an obese-microbiome and obesity later in childhood [2]. The increased levels were found in the stool samples of overweight children at the age of sevens, whereas their normal weight compared children have an significant higher Bifidobacteria count [2]. A human studies on twins revealed that the obese twin had a shift towards increased Clostridia and Firmicutes as well as increased Gammaproteobacteria and Deltaproteobacteri. When this microbiome was transplanted into germ-free mice, the fat mass increased and biomarkers associated with the metabolic syndrome were observed [13]. All these imply that these bacteria in the gut microbiome are associated with weight gain and obesity.

Infants who are born by vaginal delivery, are colonized by the microbiome in the birth canal and maternal gut microbiome, whereas infants born by caesarean delivery are initially colonized by skin flora and in some cases even hospital environment [1,4,10,12]. In babies born via caesarean delivery the stool revealed a decrease in Bacteroidetes, Bifidobacterium [2,12,17] and Lactobacillus, a rise in Clostridium species [2,15] and an overall reduction in microbiome diversity. Some of these differences maintained, in some cases, even to the age of seven [9,11]. As mentioned before, obese people have the same increased and decreased bacteria and a reduction of the diversity. This means that children who are born the natural way obtain their microbiome from their mother, whereas cesarean children obtain the

microbiome from their environment. These infants show the same microbiome phenotype as obese people.

3.3 Breastmilk, obesity and formula feeding

After birth, the child needs to be fed. Most of the woman choose to breast feed their child. The maternal breast milk not only contains components for the growth of the infant, but contains bacteria necessary for the initial microbial colonization of the infant's gut [2,10,12]. Nevertheless, not all woman can or want to breastfeed and choose for formula feeding. This could have some massive influences on the microbiome of the infant.

The most common microbes found in human breast milk are from the genera Bifidobacterium and Lactobacillus [10,12]. Although in al low concentration, but these bacteria are similar to the bacteria witch are found in the infant's gut. When comparing the composition of the breast milk from lean and obese mothers, the obese mothers have lower diversity and a distinct microbiota composition in their breast milk compared to lean mothers. Reduced Bifidobacterium count and a higher relative abundance of the groups Lactobacillus and Staphylococcus were detected in the milk samples of obese mothers [1,2,7,10,11,17]. The formula-fed infants have a decreased diversity of the genus Bifidobacterium [10,12], and this was associated with increased adiposity at the age of 18 months [10]. These infants were more often colonized with E. coli, C. difficile, Bacteroides, Enterococci, Enterobacteria and lactobacilli [7,11,12,14]. Interestingly, formula-fed infants have greater diversity of gut microbial communities relative to breastfed infants [10,11]. These infants have higher proportions of pro-inflammatory Gammaproteobacteria (C. difficile, Peptostreptococcaceae and Verrumicrobiaceae) which may suggest a slower maturation of the gut [10].

In addition, human milk contains gylcans such as oligosaccharides (HMO), glycoproteins, and glycolipids, which play a role in the modulation of the infant's microbiota development. The milk glycans promote especially the growth and activity of the Bifidobacterium and Bacteroides spp [2,8,10,12]. Higher concentrations of Bifidobacteria during infancy may provide protection against developing overweight and obesity later in life[2]. When certain bacteria metabolize the HMO's, it leads to the production of SCFA which reduce the pH of the intestinal lumen altering the microbiota profile and inhibiting pathogen growth. As mentioned earlier, the SCFA may contribute to dietary energy harvest, modulate host adiposity and alter gene expression of host satiety hormones [8], and by that leading to increased adiposity.

The breastmilk also contains the hormone leptin, what is missing in the formula feeding. Garcia-Manta et al. discussed there are human and animal studies leading to the moderate effect of leptin on the protection from weight gain. They suggest that leptin has additional downstream effects on the appetite regulation and thereby protecting for obesity later in life [11].

As mentioned before, the microbiome of obese people differs from the non-obese people, so differs the breast milk of obese mothers. It contains high levels of metabolic product such as leptin, ghrelin, adiponectin, insulin and glucose [2,11]. In addition, it contains high levels of inflammatory markers, such as IL-6 and TNF-α [11]. These changes can be important factors in the shaping of the gut microbiome of the young infant microbiome.

As discussed, the influence of the breast milk has a massive impact on the child by not only providing the child of components for the growth, but also transmits bacteria, hormones and inflammatory markers. This means that the obese mother will pass the factors related to obesity to her infants, maintaining and driving the microbiome in an obese phenotype.

4 Co-factors on the child's microbiome

As discussed in the previous chapter, there are factors who participate in the transmission of the microbiome from mother to child. There are several other factors which can make a big difference in the microbiome, but are not transmitted vertically. On of the factors discussed in this chapter will contribute to an unhealthy state, and the other can drive the unhealthy microbiome in a healthier state. Therefor, we will discus both of the factors.

4.3 Antibiotic use

As people get sick, sometimes the use of antibiotics is needed to treat the bacterial infection. During the treatment, the bacteria causing the infection are killed, but so are the bacteria in the gut. This affects the composition of the microbiome in the gut and can cause some serious alterations.

If the mother uses antibiotic in the second and third trimester, the risk of obesity for the child at the age of 7 is increased by 87%. This is due to the alterations in the maternal's microbiome by the antibiotics [15]. The use of antibiotic intrapartum had been associated with decreased bacterial diversity of the infants first stool and lower abundance of Lactobacilli and Bifidobacteria in the neonatal gut [6].

Blasers group studies the relationship between antibiotics and the microbiome. They showed that antibiotic use in mice leads to increased adiposity. In another study it was found that especially Lachnospiraceae sp. and other Clostridiales are sensitive to antibiotic use in the young infant. Disturbance the maturation of the early microbiome by antibiotics leads to an decreased α-diversity, increasing the risk of the onset of obesity later in life. The authors also found that there is al link between delayed maturation of the microbiome and antibiotic use of the infant. The Blaser group examined infants with and without antibiotic use (the other factors in these infants are the same). They found that the infants exposed to antibiotic use between the age of 6 and 12 month have a delayed maturation of the microbiome [[20]]. Other studies showed that post-natal antibiotic use in the first 12 months after birth can alter the microbiome of the infant, what is associated with an increased body weight and central adiposity early as 24 months and up to 9 years of age [1,9,16,17].

These findings explain the effect of antibiotics on the infant's gut microbiome, especially in the critical window of programming the microbiome. The limitation of these studies is that they do not provide complete information about the type of antibiotic that is used. However, the most antibiotics used in clinical settings are broad-spectrum antibiotics, which attack most of the bacteria in the gut microbiome.

4.4 Pre- and probiotic use

Most of the co-factors mentioned above are driving the microbiome of the child, from an obese mother, towards an obese phenotype. Pre- and probiotics have an opposite function, driving the microbiome in an anti-obesity phenotype. Due to their function they can disrupt the obese cycle and therefor important to mention.

In the review of Fukuda an Ohno, they described a study where overweight participants received an oral admission of Lactobacillus gasseri SBT2055 (Firmicutes pph.). They observed a decrease in subcutane and visceral fat of the abdomen in the participants. Another

study, a prospective follow-up, showed that pre- and postnatal admission of L. rhamnosus GG prevented excessive weight gain in the children [6].

They also reviewed some murine and human studies related to the effect of inulin supplementation. The inulin has an effect on the gastrointestinal hormones, such as GLP-1, ghrelin and peptide YY. Through a downstream effect these hormones affect insulin secretion and gastrointestinal motility. Therefor they can influence the anti-obese phenotype. Also, this supplementation deceased the Bacteroides intestinalis, Bacteroides vulgates, and Propionibacterium, while increasing Bifidobacterium and F. prausnitzii in obese woman [6]. Another study shows that oligofructose, a prebiotic, increases the Bifidobacteria and improves the glucose tolerance. The benefits of the oligofructose are through the pathway with GLP-1 and GLP-2. These hormones are causing decrease in glucose in the serum and promote satiety [6].

Different randomized controlled trials discussed in the review from Soderberg et al. show a benefit from receiving probiotics. With an admition of Bifidobacterium lactis alone or B. lactis plus Lactobacillus rhamnosus GG (LGG) to pregnant woman 14 days before caesarean delivery, the placenta shows an alteration in the fetus' immune system development. These bacteria increase the Bifidobacteria colonization in the infant [16,17].

As mentioned in this paragraph there are different pre- and probiotics that improve the infants gut, driving them to a healthy microbiome. Although the above pre- and probiotics are not all the compounds that can be used, it is clearly demonstrated that the obese cycle may be disrupted by admitting these to the mother of the infant or the infant.

5 Clinical outcomes for the child

Obese mothers transfer their children with the obese-typed microbiome, while the colonization of the infant's gut has an impact on the immune, metabolic and endocrine [1] systems. These children have a predisposition to suffer from the same alterations as their obese mothers like decreased insulin sensitivity, higher energy harvesting, an altered programming of the immune system and changes in the hormones and other signaling metabolites.

Bifidobacteria and Bacteriodetes play an important role in the infant gut for inhibiting the growth of pathogenic organisms, programming immunological and inflammatory responses and programming the mucosal barrier function and are found in healthy infants [11,18]. As these bacteria are decreased in the obese children, they do not have the protective and correct programming in early life leading to obesity and other diseases later in life [12,18].

The Bifidobacterium longum ensures the differentiation of the T-cells in the thymus is and the maturation of dendritic cells in the gut (add ref). This type of bacteria is also necessary for the programming of the regulation of T-cells and natural killer T-cells [1]. The decreased levels of Bacteriodetes in the altered microbiome of the infant through the first thee months predict the de high risk of overweight and obesity [8]. In addition, the Bifidobacteria secretes products witch down regulate pro-inflammatory cytokines IL-6, IL-8, CRP and INF-γ, while upregulating the anti-inflammatory cytokines IL-10. Together with Bacteroides fragilis, Bifidobacteria stimulates the secretion of IgA, witch decreased the innate immune responds giving pathogens the change to settle in the infant's gut [9,]. While being over weight, these bacteria in the infant, are decreased and the risk for auto-immune diseases increases [5].

Some studies revealed that maternal obesity had an impact on the fetal insulin resistance and glucose-insulin homeostasis. The infants of obese mothers have an increased risk of to develop insulin resistance at the age of eleven [3]. In addition, overweight children have a lower concentration of lactate in the gut, but an increased concentration of butyrate due to the obese microbiota. This increased concentration of butyrate has a downstream influence on the insulin sensitivity [6].

Another problem caused by the maternal obesity is the increased nutrition availability in the maternal system. Due to the increased nutrition availability the fetus can grow more rapidly than a normal fetus. The risks of foetal macrosomia, a condition where the child's weight at delivery is >4000g, is a twofold higher in obese woman than lean [3,16].

In a study from Kalliomaki et al. they compared the fecal samples of 25 overweight and 24 normal-weight children. The number of Bifidobacterium in the fecal samples of normal-weight children were higher during infancy and the number of staphylococcus aureus were higher in the obese children [].

As the breast milk not only contains components for the growth and bacteria, it also contains hormones and cytokines which are represented in the mother. As previously mentioned, obese mothers have an increase in pro-inflammatory cytokines [3,9,16,18] and alterations in the satisfying hormones [14,16]. These can be transmitted to the infant though the breast milk, also contributing to the obese phenotype of the infant.

The above findings conclude that the alterations in the infant's microbiome are responsible for altered pathways, such as the insulin sensitivity and an altered immune system. These alterations are the same as in obese people, giving the infant more factors for being obese and keep this phenotype.

CONCLUSIONS

Obesity is one of the biggest public health problems and there are many studies that explore the source of obesity. Although it is known that the children of obese parents have an increased risk of obesity later in life, this could not be fully explained by genetics. In most cases the first colonization of the infant's microbiome is through the vertical transmission from the mother, so it could be reasonable to assume the obese microbiome is transferred to the child. This is important to investigate, because it gives more insight into the role of the microbiome in relationship to obesity.

First of all, it is important to understand the obese microbiome. This microbiome shows a decreased number in Bifidobacteria and Bacteroidetes, an increased number Firmicutes and Proteobacteria and a lower diversity. In addition, the pregnancy induces a shift in the microbiome, driving the microbiome to the same shift as seen in obese people's microbiome. Moreover, there are altered pathways seen in the mother assiciated to this microbiome, such as decreased insulin sensitivity, increased body fat, promoting pro-inflammatory cytokines, increased energy harvesting and alterations in satiety metabolites and hormones.

The same bacterial shifts are seen in obese and overweight infants, suggesting that the mother's obese microbiome colonized the infant's gut. The way of delivery and breastfeeding have an important role in this transmission, contributing to the obese microbiome. The breast milk of obese women contains different bacteria, cytokines and hormones driving the infant's gut microbiome toward an obese state. The use of antibiotics is not directly involved in the transmission, but has a critical impact on the young microbiome driving it to an unhealthier state. On the other hand, pre- and probiotics can drive the obese microbiome towards a healthy state, making them useful to disrupt the obese cycle.

In final words, the obese state of the mother is affecting her offspring through the transmission of the microbiome. This affects the infant's microbiome in a way that it is driven towards an unhealthy state, making the infant very sensitive to being obese. A next step is to investigate how this obese cycle can be disrupted at a young age, preventing infants from becoming overweight and obese later in life.

REFERENCES

[1] Holmes E., Li J.V., Marchesi J.R. and Nicholson J.K. (2012).Gut Microbiota Composition and Activity in Relation to Host Metabolic Phenotype and Disease Risk. Cell Metabolism 16: 559-564

[2] Tschöp M.H., Hugenholtz P. and Karp C.L. (2009). Getting to the core of the gut microbiome. Nature Biothechnology 27(4):344-346

[3] Gohir W., Ratcli E.M. and Sloboda D.M. (2015). Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pedeatric Research 77(1): 196-204

[4] Kinross J.M, Darzi A.W. and Nicholson J.K. (2011). Gut microbiome-host interactions in health and disease. Genome medicine 3(14)

[5] Envgen group (n.d). Metagenomic 101. From http://envgen.github.io/metagenomics.html

[6] Fukuda S. and Ohno H. (2014). Gut microbiome and metabolic diseases. *Semin Immunopathol* 36:103–114

[7] Tremaroli V. and Bäckhed F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature* 489: 242-250

[8] Laursen F.M., AndersenL.B.B., Michaelsen K.F., Mølgaard C., Trolle E., Bahl M.I. and Licht T.R. (2016). Infant Gut Microbiota Development Is Driven by Transition to Family Foods Independent of Maternal Obesity. mSphere, 1 (1)

[9] Houghteling P.D. and Walker W.A. (2015). Why Is Initial Bacterial Colonization of the Intestine Important to Infants' and Children's Health? *JPGN* 60(3):294-307

[10] Anne L. Dunlop, Jennifer G. Mulle, Erin P. Ferranti, Sara Edwards, Alexis B. Dunn, Elizabeth J. Corwin. (2015). The Maternal Microbiome and Pregnancy Outcomes that Impact Infant Health: A Review. *Advanced Neonatal Care* 15(6): 377-385

[11] Garcia-Mantrana I. and Collado M.C. (2016). Obesity and Overweight: Impact on Maternal and Milk Microbiome and their Role for Infant Health and Nutrition. *Molecular Nutrition & Food Research*

[12] Serino M., Nicolas S., Trabelsi M. S., Burcelin R. and Blasco-Baque V. (2016). Young microbes for adult obesity. *Pedeatric Obesity*

[13] Soderberg, T. K., Borengasser, S. J., Barbouw, L. A., & Friedman, J. E. (2016). Microbial transmission from mothers with obesity or diabetes to infants: an innovative opportunity to interrupt a vicious cycle. *Diabetologia* (59): 895-905

[14] Omry Koren, Julia K. Goodrich, Tyler C. Cullender, Ayme´ Spor, Kirsi Laitinen, Helene Kling Backhed, Antonio Gonzalez, Jeffrey J. Werner, Largus T. Angenent, Rob Knight, Fredrik Backhed, Erika Isolauri, Seppo Salminen and Ruth E. Ley.Host (2014). Host

Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy. *The Cell* 150:470-480

[15] Mueller N.T., Bakacs E., Combellick J., Grigoryan Z. and Dominguez-Bello M.G. (2015). The infant microbiome development: mom matters. *Trends in Molecular Medicine* 21(2): 109-118

[16] O'Reilly J.R. and Reynolds R.M. (2013). The risk of maternal obesity to the long-term health of the offspring. *Clinical Endocrinology* 78:9-16

[17] Koleva P.T., Bridgman S.L. and Kozyrskyj A.L. (2015). The Infant Gut Microbiome: Evidence for Obesity Risk and Dietary Intervention. *Nutrients* 7:2237-2260

[18] Vangay P., Ward T., Gerber G.S. and Knights D. (2015). Antibiotics, Pediatric Dysbiosis, and Disease. *Cell Host & Mircobe* 17:553-565

[19] Backhed F., Roswall J., Peng Y., Feng Q., Jia H., Kovatcheva-Datchary P., Li Y., Xia Y., Xie H., Zhong H., Khan M.T., Zhang J., Li J., Xiao L., Al-Aama J., Zhang D., Lee J.S., Kotowska D., ColdingC., Tremaroli V., Yin Y., Bergman S., Xu X., Madsen L., Kristiansen K., Dahlgren J. and Wang J. (2015). Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host & Microbe* (17):690–703

[20] Bokulich N.A., Chung J., Battaglia T., Henderson N., Jay M., Li H., Lieber A.D., Wu F., Perez-Perez G.I., Chen Y., Schweizer W., Zheng X., Contreras M., Dominguez-Bello M.J. and Blaser M.J. (2016). Antibiotics, birth mode, and diet shape microbiome maturation during early life. Science Translational Medicine 8 (343): 343-382