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MICROBIOTA – OBESITY: ASSOCIATIONS FROM MOUTH TO GUT ACROSS ALL AGES

M. Joossens[1], D. Vandeputte[2-4], N. Michels[5]

[1]Department of Biochemistry and Microbiology (WE10), Laboratory of Microbiology, Ghent University, Ghent, Belgium
[2]Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven – University of Leuven, Leuven, Belgium
[3]VIB, Center for Microbiology, Leuven, Belgium
[4]Cornell University, Meinig School of Biomedical Engineering, Ithaca, NY, USA
[5]Department of Public Health and Primary Care, Ghent University, Belgium

Corresponding Author: Marie Joossens, Ph.D; marie.joossens@ugent.be

Abstract: In this paper, we give an integrated overview of the most recent insights regarding the role of the microbiota in obesity across body-sites for different age groups based on observational and interventional data published between April 2019 and March 2020.

Keywords: Microbiota, Child, Adult, Oral, Faeces, Integromics, Metabolomics, Obesity, Ethnicity.

INTRODUCTION

More than a decade ago, Turnbaugh et al[1] demonstrated a causal role of gut bacteria in obesity, initiating an expansion of microbiome research in this field. The initial emphasis on gut bacteria has since evolved to currently cover different microbial kingdoms and more body-sites.

This paper gives an overview of the most relevant recent findings on the role of the microbiota in obesity, separating results regarding life stage, given the profound influence of age on microbiota composition. It covers a range of sample-types (e.g., faeces, fat tissue, saliva, blood), omics data (e.g., microbiome, metabolome and human genome data), and microbial kingdoms, in order to give a broad summary of the latest results.

First, we discuss novel findings regarding the microbiota-obesity link based on observational studies in adults, with a focus on results obtained through large-scale studies. Next, we summarize the newest data in children and highlight the overlap in microbiota signals between different age-cohorts. Lastly, we discuss insights from interventional studies using pro- and synbiotics, or faecal microbiota transfer (FMT) in light of the state-of-the-art on microbiota obesity-associations.

OBSERVATIONAL STUDIES IN ADULTS

Over the past years, several studies fine-tuned earlier findings on altered faecal microbiome composition in obesity. The newest data substantiates the inverse relation between bacterial diversity and obesity[2-5], but indicates it to be specific for non-Hispanic white populations and/

or high socioeconomic status[4]. Results of a small study including only obese subjects of different geographic locations are in line with these observations, reporting higher richness in the non-Western populations (i.e., French Polynesia and Amazonian French Guiana)[6].

Concerning ethnic differences in microbiome disease signatures, the association of high *Prevotella* abundance with high BMI was confirmed once again in a Hispanic population[2] and appears to be more pronounced in subjects with black or Hispanic ethnicity[4]. A Spanish study[7] on obesity in the elderly however reported the inverse correlation with three-fold higher relative *Prevotella* abundances in non-obese compared to obese subjects. Combined, these observations indicate the need for large cohort studies focusing on non-white populations and obesity.

More in-depth analyses of microbiome composition fortified previously observed associations between bacterial abundances and obesity up to species level (Figure 1), with conflicting results for *Blautia* that was inversely correlated to visceral fat[8] and to BMI[3], yet positively associated to visceral fat according to a third study[9]. Analyses of the functional capacity of the microbiome using shotgun sequencing on a subset of lean versus obese subjects, revealed decreased capacity for unidirectional conjugation as well as superoxide reductase. The latter is in line with hypothesized increased oxygen stress induced by microbial dysbiosis and subsequent weight gain[5].

Integromics on Gut Bacteria and Obesity

During the past years, Visconti et al[10] reported findings on the interaction between gut microbiome and host metabolism by integrating intestinal microbiome, blood and faecal metabolomics data. They corroborated earlier reports on depletion of *Methanobrevibacter smithii* in obesity by revealing a negative association between *M. smithii* and visceral fat. Also, blood threonate was negative associated to measures of adiposity and this blood metabolite was directly and indirectly associated to faecal abundance of *M. smithii*.

Kayser et al[11] linked fasted serum with faecal microbiome composition and found decreased abundance of *Methanobrevibacter smithii* and *Bifidobacterium adolescentis* among others, to be associated with low gene richness and high serum levels of lipids (ceramides). *Ruminococcus gnavus* was positively associated with sphingosine-containing ceramides in blood. Further functional microbiome analyses uncovered a positive association between microbiome synthesis capacity of two pathogen-associated molecular patterns, i.e., lipopolysaccharide and flagellar assembly, and ceramide levels.

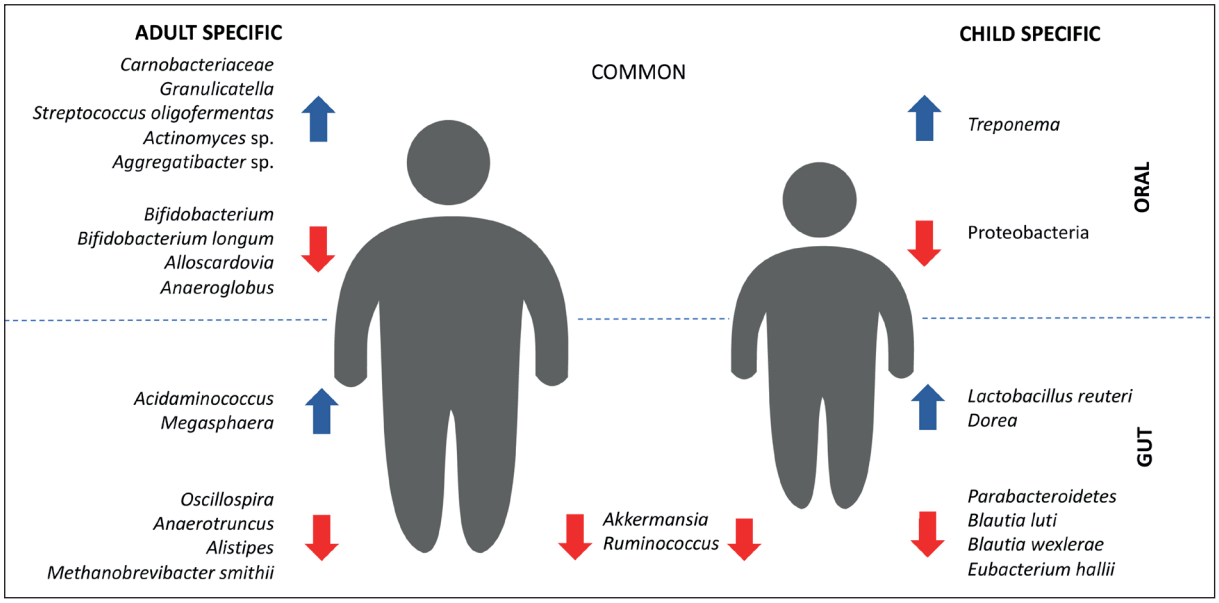

Figure 1. Latest consensus results on links between microbiota and obesity in adults and children.

Analyses of associations between serologic metabolites and intestinal microbiome composition in obesity on subsets of the PopGen and FoCus cohorts revealed that significant associations displayed different patterns in lean and obese individuals5. Overall, serologic metabolites and gut microbiome composition were significantly associated with each other, but serum metabolites had marginal effect sizes on microbiota compositional variation.

The combined analyses of host genotypes, intestinal microbiome and faecal short-chain fatty acid levels in normoglycemic individuals[12] revealed a host-genetic-driven increase in intestinal production of butyrate to be associated with improved insulin response, whereas abnormalities in propionate management were causally related to higher type II diabetes risk.

A small study also contrasted DNA methylation patterns in blood and visceral adipose tissue in obese subjects with low versus high Bacteroidetes/Firmicutes ratio[13]. They found two candidate genes implicated in glucose and energy homeostasis, *HDAC7* and *IGF2BP2*, to be hypomethylated and overexpressed in adipose tissue in the low Bacteroidetes/Firmicutes ratio group. This suggests the epigenetic regulation of these genes by gut bacteria. Furthermore, the comparison of morbid obese individuals with and without type 2 diabetes[14], revealed a higher number of observed OTU's in mesenteric adipose tissue of obese non-diabetic patients.

Mycobiome – Obesity Associations

In their study on the Hispanic population in the USA, Kaplan et al[2] assessed the faecal mycobiome in relation to obesity. Fungal microbiota composition based on ITS1 sequencing was not associated with obesity and none of the 23 predominant fungal genera was differentially abundant in the obese individuals. Oral health status, more specifically the number of missing teeth in subjects, explained most of the diversity in mycobiome composition, indicating the value of an integrative perspective. To solve the puzzle of how human-associated microbiota cause disease, the assessment of microbiota interactions across sample sites might speed up the process.

Oral Microbiota – Obesity Associations

A large study[15] focusing on the relation between the oral microbiota and obesity in an African-American population revealed a strong inverse relation between both *Bifidobacterium* at genus level, and *Bifidobacterium longum* at species level, and the prevalence of obesity. Zooming in on potential probiotic species showed lower prevalence of all observed species from the genera *Bifidobacterium* and *Lactobacillus* in obese subjects. Seven other taxa were associated with increased prevalence of obesity after multiple testing correction, of which *Granulicatella adiacens*, *Streptococcus oligofermentas*, *Actinomyces* sp. oral taxon 180 and *Aggregatibacter* sp. oral taxon 512, could be assigned up to species level. Two rare oral genera, *Alloscardovia* and *Anaeroglobus*, were associated with decreased obesity prevalence. Community-based clustering further identified 14 different clusters, with one cluster of 7 OTUs being associated with decreased risk of obesity. Six out of 7 of these OTUs were assigned to species of the *Lactobacillus* genus, among them *L. reuteri*. Of note, no heterogeneity among the ethnic groups was observed.

OBSERVATIONAL STUDIES IN CHILDREN

Gut Microbiota – Obesity Associations

Overweight, and therefore also the associated comorbidities, has high prevalence rates in children. Due to its high resistance to treatment, vigilance and early prevention is appropiate[16]. According to a study in 3 years old infants, several taxon-overweight correlations were similar in children and adults[17], suggesting that changes in the gut microbiome in early childhood may predispose children to obesity in adulthood. As obesity stimulating lifestyle factors

were not associated with the most abundant genera, the overweight microbiota signature seems directly linked to overweight. Still, longitudinal studies are necessary since bidirectional links between microbiota and obesity-risk factors like diet and stress are possible[18].

A large study in 6-12 years old focusing on *L. reuteri*[19] found positive correlations with BMI and waist circumference, as has been reported for adults as well. More specifically, they discovered indirect effects through adiposity on insulin resistance and hyperlipidaemia. Probiotic use of *L. reuteri* as immune regulator might thus have undesired side effects like adiposity. However, a patented *L. reuteri* strain was able to decrease 2 of the 16 tested inflammatory parameters and seemed not to influence weight status and lipid homeostasis (but statistics were not fully reported)[20].

A recent cross-sectional study revealed that two *Blautia* species with anti-inflammatory potential were depleted in obese children. As the effect was more pronounced in combination with insulin resistance, it emphasizes the microbiota interaction with metabolism and inflammation[21].

Oral Microbiota – Obesity Associations

The most remarkable study[22] of the past year on the oral microbiota is based on a crowdsourced US population cohort that compared the sequenced oral microbiota from 8-16y old children versus adults and assessed associations with lifestyle factors. It confirmed differences in composition over age groups, namely a more diverse microbiome in youth versus adults and less intra-group variation. Adult and youth oral microbiome were influenced mostly by oral health habits and sex or weight respectively. In youngsters, a higher BMI was linked with higher oral microbial diversity, which contrasts findings in adults[22,15] but is in agreement with a recent child study[23], suggesting age-specific microbial patterns for obesity. In obese youth, a higher abundance of *Treponema* species was furthermore observed[22]. In adults, *Treponema* has been associated with poor oral health, a condition often observed in obese individuals.

Salivary bacteria may play alternative roles in obesity, through their involvement in taste sensitivity, appetite regulation and insulin resistance, as well as metabolic efficiency[24]. A recent study[23] in 6-14 years old children showed oral bacteria might influence taste by the production of components near taste receptors. In line with results in adults[24], obese children had lower taste sensitivity and might thus need larger amounts to elicit a taste response. Furthermore, the decreased Proteobacteria in obese children seemed to be linked to low taste sensitivity. Independent from BMI, high oral Bacteroidetes abundance seemed to comprise those with less bitter taste sensitivity[23]. Of note, the crowdsourced population study could not relate taste preference to the oral microbiome[22].

MICROBIOTA INTERVENTIONS AND OBESITY

Obesity Related Microbiota Interventions in Adults

Given the many roles of microbiota in obesity, it is a potential therapeutic or preventive medium for obesity complications. Last years' publications included interventions with selected microbiota (probiotics supplementation)[20,25-29], prebiotic foods[30], synbiotics[31] or antibiotics[32], and two reviews on FMT in obesity became also available[33,34].

A systematic review[33] on FMT summarized three placebo-controlled studies in obesity and reported no effect of FMT on BMI and mixed effects on other metabolic endpoints. In adults, a meta-analysis concluded that probiotic supplementation results in a reduction of adiposity (BMI, waist or fat percentage) together with improvements in several glucose and lipid homeostasis parameters[35]. Interventions towards obesity conducted in the past years often used diverse, multi-strain[26,27,29] probiotics. Remarkably, interventional microbiota changes were sometimes not tested[29] or were non-existent to very subtle[25,27,31]. However, one study reported on decreased TM7 which are positively linked with adiposity, and increased Clostridiaceae which are negatively linked with inflammation upon probiotic intervention with a mixture of

lactobacilli and bifidobacterial strains[26], which highlights the relevance of overall reporting microbiome changes. For the first time, *Akkermansia muciniphilia* was tested in a human intervention trial proving its safety and potential to improve anthropometric parameters[25].

Microbiota-based interventional studies in obesity are still inconclusive. To reduce heterogeneity between studies, guidelines on a minimal core set of variables to include in obesity intervention studies have been published this year[36]. These proposed guidelines will allow stronger meta-analyses for future studies.

Obesity Related Microbiota Interventions in Children

Childhood may provide opportunities to promote health or prevent disease through microbiome interventions. A recent meta-analysis on randomised placebo-controlled trials in overweight children, found no effect on weight (BMI, fat percentage or waist circumference), lipid or glucose homeostasis after supplementation with pro-/synbiotics for 4-16 weeks[37]. However, restricting the meta-analyses to the two synbiotic interventions revealed a reduced BMI z-score. The lack of weight loss upon probiotic supplementation was also observed in a recent randomised placebo-controlled trial using *Bifidobacterium pseudocatenulatum* CECT 7765 in obese 10-15y olds with insulin resistance, despite an improvement in inflammatory status and HDL status[38]. Thus, probiotics towards overweight treatment seem to be less successful in children. However, probiotic interventions might need more time to affect weight status in growing children *via* gradual changes in gut microbiota. After all, the study using the *Bifidobacterium pseudocatenulatum* CECT 7765 probiotic showed no effect on *Bifidobacterium* abundance but showed increased *Alistipes* abundance, a genus previously detected in lean phenotypes[38]. Even without effects on anthropometrics, potential effects of probiotics on prevention of early atherogenic or cardiovascular damage in high-risk groups should be considered, both in children and adults[27].

CONCLUDING REMARKS

In the past years, promising observational and therapeutic results confirmed the importance of the link between microbiota and obesity in both children and adults. Herein, most breakthroughs were obtained *via* integrated analyses of different omics in large cohorts. These integromics analyses encourage follow-up research, specifically with respect to the role of the archaeon *M. smithii* in obesity. Also, ethnicity-based differences in microbiota-obesity patterns have become apparent. The further confirmation of these observations will have important implications for microbiota-based prevention, monitoring and treatment of obesity and related diseases. Despite its advantages for discriminative power, data stratification are not yet well-established in intestinal microbiome research. Based on the current findings, however, stratifying on ethnicity in microbiome-related research on obesity might increase discriminative power.

Current conflicting results on relations between bacteria and obesity on genus-level might be illustrative for a technical boundary in microbiome research, signalling that more in-depth analyses of the microbiota are needed to force further breakthroughs. After all, both pathogenic potential and health-enhancing properties are known to be strain-specific. By further detailing microbiome results to species and strain-level information, the present contradictions at genus level could disappear. Alternatively, if the prevailing trend of microbial differences based on ethnic background is being confirmed, these differences might likewise translate in different microbial signatures for the same disease in different patient groups.

Finally, the intriguing results on oral bacteria and taste perceptions might open new alleys for obesity prevention and treatment. If oral bacteria are confirmed to change taste perceptions and thus hedonic satisfaction from smaller food portions, it is worth looking into it to improve diet adherence in obesity.

Conflict of Interest

MJ, DV and NM have no conflict of interest.

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