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Review

Microbiota manipulation for weight change

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A B S T R A C T

Manipulation of the intestinal microbiota has been linked to weight changes and obesity. To explore the influence of specific agents that alter the intestinal flora on weight in different patient groups we conducted a meta-analysis of randomized controlled trials (RCTs) reporting on the effects of probiotics, prebiotics, synbiotics, and antibiotics on weight. We searched the Pubmed and Cochrane Library databases for trials on adults, children, and infants evaluating the effects of these substances on weight. Our primary outcome was weight change from baseline. Standardized mean differences (SMDs) with 95% confidence intervals were calculated.

We identified and included 13 adult, 17 children, and 23 infant RCTs. Effects were opposite among adults and children, showing weight loss among adults (SMD −0.54 [−0.83, −0.25]) and minor weight gains among children (SMD 0.20 [0.04, 0.36]) and infants (SMD 0.30 [−0.01, 0.62]) taking mainly *Lactobacillus* probiotic supplements. Heterogeneity was substantial in the adult and infant analyses and could not be explained by intervention or patient characteristics. Azithromycin administration in children with pulmonary disease was associated with weight gain (SMD 0.39 [0.24, 0.54]), without heterogeneity. A high risk of selective reporting and attrition bias was detected across the studies, making it difficult to draw firm conclusions. Overall, our meta-analysis suggests that there may be a role for probiotics in promoting weight loss in adults and weight gain in children, however additional studies are needed. Though we cannot recommend antibiotic administration for weight manipulation, its use provides advantageous weight gain in children with cystic fibrosis and bronchiectasis.

Contents

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1. Background

The rising prevalence of obesity among children and adults and its harmful associations are of increasing global concern [1,2]. Attempts to understand the etiology of this growing problem have highlighted the combined influences of environmental, genetic, and hormonal factors on weight gain and obesity [3–11]. Newer studies have also implicated the microbial gut composition in contributing to this epidemic [12–15]. Some of the first experiments exploring the relationship between the gut microbiota and obesity found that germ-free mice, which are leaner than conventional mice, display increases in body fat, intestinal monosaccharide absorption, and production of liver triglycerides upon introduction of cecum-derived feces from conventional donor mice [14]. Subsequent research in humans and mice revealed that gut microbial communities influence caloric intake, intestinal absorption, and energy balance and that these features are transmissible though microbiota transplantation [16,17]. This sparked the beginning of deeper investigations to further unveil the relationship between the gut microbiota and obesity.

More recent studies have since observed a reduction in species diversity in the microbiota of obese compared to lean individuals [17,18]. Additional experiments implicated specific microbial species in relation to weight gain or loss. Historically, higher proportions of *Bacteroidetes* species relative to *Firmicutes* species have been correlated with a leaner status in humans [17]. Nowadays, identification of microbiota at the species and strain level allow for finer associations between bacteria and weight. Although the diversity on the species level was profound among the subjects in this study, the results were still representative as these two divisions made up over 90% of the microbiota [17]. Pro-, pre-, synbiotics, and antibiotics have also been reported to change microbiota composition [19,20]. As a result, these supplements have been hypothesized to help treat obesity and malnourishment clinically by triggering changes in the microbial community [21,22]. Studies employing certain probiotic regimens in adults to combat obesity have indeed found them to promote weight loss in diet-induced obesity [23] and to enable prevention and treatment of obesity [24]. Furthermore, the combined use of prebiotics with probiotics containing species that are associated with leaner hosts has been proclaimed to augment these effects by enhancing the nourishment and activity of the microbiota [19,20,25].

Simultaneous to investigation of their potential use in weight loss, pre-, pro-, and synbiotics have been utilized to induce weight gain in neonates and malnourished children [26–28]. Some randomized control trials have succeeded in promoting growth and improving nutritional status of infants by introducing probiotic supplements into formula [28,29], whereas many have shown no effect [27,30–32]. Antibiotic use has also been proposed to induce weight changes through its effects on microbiota [33]. Studies in animals, children, and adults have correlated the use of certain classes of antibiotics, including macrolides and tetracyclines, with weight gain and obesity [33]. However the question remains as to whether these effects are due to improved health status in these patients or the result of changes in the gut microbiota.

This meta-analysis aims to review the evidence available on the effects of microbiota manipulation using microbes (probiotics) or drugs that affect the microbial communities of the gut (prebiotics and antibiotics). Thus, we plan to include only randomized controlled trials (RCTs) assessing the effects of these additives on body mass index (BMI) and weight change in neonates, children, and adults of normal, obese, or underweight status. The effects are likely heterogeneous and depend on the type of additive, the duration of its administration and the host. Conclusions from this study can provide insight into the potential clinical use or implications of utilizing agents that affect the microbiota.

2. Methods

We compiled RCTs that explored the effects of microbes (probiotics) or other substances that influence the microbiota (prebiotics, synbiotics, antibiotics) on BMI or weight.

2.1. Study inclusion and exclusion criteria

Types of studies: We included RCTs and cross-over RCTs if they reported outcomes at the end of the first cross-over period.

Types of participants: Adults (18 years and above), children (2–18 years), and infants (1 month to two years of age) with normal, obese or lean weight at baseline were included. Subjects with inflammatory bowel disease, colitis, *Clostridium difficile* infection, diarrhea and other disturbances of the gastrointestinal tract at baseline that might mask the effects of microbiota modulation were excluded. Pregnant women, preterm babies and neonates were also excluded as the effects are likely to differ in these patient groups. In studies that recruited infants from birth, we included those that continued the intervention for the minimal defined duration from 1 month of age. In addition, subjects with HIV were excluded following studies suggesting that these individuals experience greater effects of probiotics/synbiotics than uninfected controls [34,35].

Types of interventions: Interventions that affects the GI microbiota composition, including any antibiotic, probiotic, prebiotic or symbiotic were included. Studies in which the probiotic bacterial species was not defined to the level of the bacterial species or the prebiotic or antibiotics contents were not clearly described were excluded. Only trials comparing intervention vs. placebo and that had an intervention period of 14 days or longer were included with the assumption that shorter durations would not affect weight in the long-term. Inhaled interventions were excluded. Comparisons between different interventions, doses or administration schedules were excluded. If multiple interventions (e.g. different doses or