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Review

The gastrointestinal microbiota and multi-strain probiotic therapy: In children and adolescent obesity

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ABSTRACT

Childhood obesity is a predisposing factor for chronic diseases both in the adolescent years and into adulthood. Current research efforts have focused on host and environmental factors that may affect energy balance. This has lead to a plausible, biological postulation that an *obese microbiota* profile may exist and may demonstrate increased energy yielding behaviour by such bacteria. Consequently, the gastrointestinal tract (GIT) microbiota is gaining significant research interest in relation to obesity in an attempt to better understand the aetiology of obesity and potentially new methods of treatment. It is now well known that the microbiota that colonise the GIT perform a number of functions that include regulating the normal development and function of the mucosal barriers; assisting with maturation of immunological tissues, which in turn promotes immunological tolerance to antigens from foods, the environment, or potentially pathogenic organisms; chemical communication and influence of target tissues such as the liver, brain, muscle, adipose tissue, heart and GIT; preventing propagation of pathogenic microorganisms as well as controlling nutrient uptake and metabolism. Here we develop a hypothesis that multi-strain probiotics may provide a potential therapeutic role when supplemented conjointly with lifestyle interventions for obese children/adolescents. The administration of multi-strain probiotics in conjunction with lifestyle measures may rescue the GIT obese microbiome phenotype and encourage the re-establishment of a microbiome towards one that resembles that of lean individuals.

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1. Introduction

In humans, following birth, bacteria colonise all body mucosal and extra-mucosal tissue sites that include the GIT, mouth, hair, nose, ears, vagina, lungs and skin, thereby giving rise to site-specific unique microbiota communities.[1] The human metagenome has been reported to consist of *Homo sapiens* genes and the

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genes that are present in the microbes that colonise and inhabit the human body.[2] Hence, the bacterial cohort in addition to contributing cues that allow for the maturation of immune tissues and function to provide immunological tolerance, also encode for metabolic capacity that in conjunction with the human host work to provide metabolites and energy balance.[3] Many of these metabolic activities still remain to be elucidated. This review considers the links between GIT dysbiosis and obesity and the metabolic sequalae that may ensue as well as the potential adjuvant role that probiotics may have in rescuing an obese-prone phenotype in adolescence.

2. Methodology

A systematic search of the literature was conducted using PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE and CINAHL.

2.1. Search terms

Articles were identified using the search terms, ''Obesity'' OR ''Overweight'' OR ''Nonalcoholic Fatty Liver Disease'' OR ''Nonalcoholic Steatohepatitis'' OR ''Steatosis'' AND ''Probiotics'' OR ''Commensal Bacteria'' AND ''Children'' OR ''Adolescents'' OR ''Adults.''

The Inclusion criteria for this review were: (1)An RCT and/or cross-over clinical trial that used either a placebo comparator or other as a control; (2) Human participants diagnosed with or without fatty liver disease; (3) Other epidemiological observational studies and (4) The clinical study was published in English. The overall body of evidence (based on a summary of the individual studies is presented in Table 2.

2.2. Composition of the GIT microbiota in overweight children and adolescents

Several observational studies have reported differences at the phylum and genera levels of the GIT microbiota in children and adults, depending on weight status or energy intake. A recent meta-analysis of the obesity-associated GIT microbiota found a consistent difference in *Bifidobacteria* genera (*Actinobacteria* phyla) numbers between 159 obese and 189 control subjects (adults and children) from 6 published studies with low heterogeneity, showing obese subjects were significantly depleted in *Bifidobacteria*. For *Lactobacillus* (*Firmicutes* phyla), no consistent or significant summary effect could be found when comparing obese to control subjects [4]. Research investigating microbial phyla associated with obese and lean individuals remains inconclusive. In terms of bacterial phyla, abundant *Firmicutes* and decreased *Bacteroidetes* have been associated with obese phenotypes [5–8] with a decreased *Firmicutes/Bacteroidetes* ratio being directly related to weight loss. Schwiertz et al. [9], however found a significant increase in the proportions of *Bacteroidetes* in obese and overweight individuals, compared to lean individuals. Arumugam et al. [10], though could not detect any correlation between body mass index (BMI) and the *Firmicutes/Bacteroidetes* ratio and therefore could not contribute to understanding the relationship between bacterial ratios and obesity. The authors concluded that the link between obesity and the microbiota is likely to be more sophisticated than the simple phylum-level *Bacteroidetes:Firmicutes* ratio that was initially identified [4,10].

Epidemiological investigations of GIT bacteria in relation to paediatric obesity are limited. In 2009, two studies in adolescents (13–15 years) reported that a lifestyle intervention based on a calorie-restricted diet and increased physical activity, induced changes in the GIT microbiota profile of obese individuals, which correlated to body weight (BW) loss and BMI reductions [11,12]. *Bacteroides–Prevotella* genera increased after the intervention in those subjects that experienced significant weight reductions (>4 kg BW) while genera belonging to the phylum *Firmicutes* such as *Clostridium histolyticum, Clostridium lituseburense* and *Eubacterium rectale–Clostridium coccoides* decreased significantly [11]. Moreover, reductions in the proportions of *C. histolyticum and E. rectale-C. coccoides* were significantly correlated with weight loss in the whole cohort [11]. Santacruz et al. [12] however found *Lactobacillus, Bifidobacterium*, *Bifidobacterium breve*, and *Bifidobacterium bifidum* counts were significantly lower in adolescents with weight reductions of >4 kg, before and after a dietary intervention program than in adolescents with weight loss of <2 kg [12]. This study demonstrated that there are different species related with weight loss. In the genus *Bifidobacterium* and *Clostridium*, some species decreased (*B. bifidum, B. breve, C. coccoides*) while others increased (*B. catenulatum, C. leptum*) significantly in the high weight loss group than in the low weight loss group after the intervention. This study suggested that the effectiveness of the lifestyle intervention on BW loss could be influenced by the composition of the individual's microbiota [12].

Furthermore, Kalliomäki et al. [13] reported that differences in the intestinal microbiota may precede developing excess weight in a prospective follow-up study. Forty-nine children were examined at birth and then at intervals up to 24 months of age and then followed–up at 4 and 7 years [13]. At the age of 6 and 12 months, GIT microbiota composition was analysed with BMI being calculated at 7 years. Of the children selected, 25 were obese and 24 were normal weight at the age of 7 years. *Bifidobacteria* numbers in faecal samples during infancy were higher in children remaining normal weight than in children becoming overweight, while *Staphylococcus aureus* was higher in children who developed obesity than in normal weight children. The study concluded that an aberrant compositional development of the GIT microbiota may precede weight gain in children. In contrast, Vael et al. [14] found that low faecal *Staphylococcus* and a high *Bacteroides fragilis* concentrations in infants aged between 3 weeks and 12 months old was associated with a higher BMI in preschool children [14]. A recent study designed to investigate the GIT microbiota in preschool children (4–5 years old) with and without being overweight or obese, demonstrated that the gut microbiota differed among preschool children who were either overweight or obese as compared to children with a BMI in the normal range [15]. Concentrations of gram-negative bacteria such as *Enterobacteriaceae* was significantly higher in the obese/overweight children, whereas levels of *Desulfovibrio* and *Akkermansia muciniphila*-like bacteria were significantly lower in the obese/overweight children.[15]

2.3. Obesity and metabolic syndrome in children and adolescents

Childhood health and well-being is adversely affected by the accumulation of excessive adipose tissue [16]. Obesity is considered a worldwide epidemic and a critical public health dilemma. In 2004 the World Health Organization (WHO) estimated that around 22 million children (<5 years old) were overweight or obese and according to the International Obesity Task Force, a total of 155 million school-aged children (5–17 years old) were overweight or obese [17]. The number of overweight and obese children and adolescents in Australia has increased significantly over the last two decades. Data from the 2004–2005 National Health Survey indicates that close to three in every 10 Australia children were overweight or obese. Therefore, in accordance with the Australian Preventative Health Task force in 2009, an estimate of 20–25 per cent of the childhood population is overweight or obese and the