The Hidden Culprit:

Predisposition to Obesity as a Result of Early-life Antibiotic Exposure

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Abstract

Background: It has been reported that the use of antibiotics is associated with excessive weight gain or obesity in healthy infants. Current data suggest intestinal microbiota perturbation caused by antibiotic exposure in the perinatal period programs the host to assume an obesity-prone metabolic phenotype. However, there is a lack of evidence regarding the causal pathway given the multifactorial etiology of obesity.
Objective: The objective of this study was to explore the significance of the association between antibiotic exposure during critical periods of infancy before the age of 2 and the development of obesity.
Methodology: A structured literature review was conducted on databases Medline, Scopus, CINAHL and Google Scholar resulting in 8 pertinent articles. Queries "Infants AND Obesity AND Antibiotic Exposure AND Gut Microbiota" were searched and screened, and infants' ages were restricted to 1-23 months.
Results: Antibiotic exposure during critical periods of early development significantly influenced weight gain and the progression of obesity. Furthermore, marked differences in the composition of their microbiota were exhibited when compared to lean subjects. Few studies concluded that exposure was not consistently associated with increased body mass, while others restricted the association solely to male infants.
Conclusion: Over-prescription of antibiotics during infancy not only causes resistance to potentially harmful organisms in the GI tract, but may also lead to a life-long risk for obesity by destroying healthy colonization of necessary bacteria. It is paramount that further research be performed in order to establish preventive measures of obesity and counteract unfavourable effects on microbiota.

Research Question

Is there a significant association between antibiotic exposure during critical periods of infancy before the age of 2 and the development of obesity?

Introduction

Childhood obesity is among the most urgent public health issues of the pediatric population.[1] Over the last 25 years, there has been a considerable rise in the number of Canadian children and youth who are overweight or obese.[2] Based on the World Health Organization guidelines, 31.5% of 5- to 17- year olds, an estimated 1.6 million Canadian children, were classified as overweight (19.8%) or obese (11.7%) from 2009 to 2011.[3] Furthermore, overweight and obese children are at a high risk of becoming obese adults as well as presenting adverse health consequences, which include cardiovascular disease, type 2 diabetes and several cancers.[4,5,6]

Since the 1940s, antibiotics have been essential in reducing human morbidity and mortality.[7] However, recent studies have shown that increased susceptibility to obesity later in life has been associated with early exposure to antibiotics in healthy individuals.[8] Worldwide, antibiotics are among the most frequently used pharmaceuticals in infants and children.[9] By two years of age, children have on average received nearly three courses of antibiotics.[9] Antibiotics are often prescribed inappropriately despite a significant number of expert guidelines which advocate its limited use.[6] It has been estimated that 5% of neonates have received antibiotics, although the incidence of culture-proven sepsis in newborn infants is less than one in 1000 neonates.[9]

As opposed to the relatively stable microbiota of an adult, the microbiota of an infant is considerably more variable and vulnerable to antibiotic perturbation.[7] The critical period of gut colonization appears in early postnatal life.[1] Thus, early administration of antibiotics may disrupt patterns of intestinal colonization and increase intestinal permeability (Figure 1).[7] Moreover, the host assumes an obesity-prone metabolic phenotype which alters the host's response to specific microbial signals.[10] Although an association between antibiotic exposure and obesity in healthy infants and children has been reported, there is a lack of evidence regarding the exact causal pathway given the multifactorial etiology of obesity.[11,12]

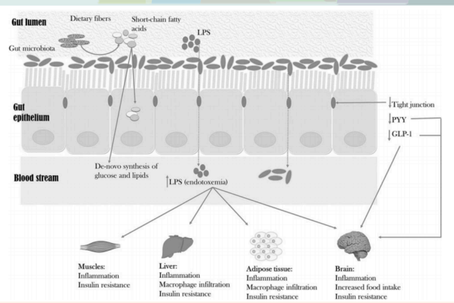

Figure 1. Increased intestinal permeability resulting in higher levels of lipopolysaccharides in systemic circulation, leading to a low-grade systemic inflammatory state.[13]

Methods

Methodology used: structured literature review

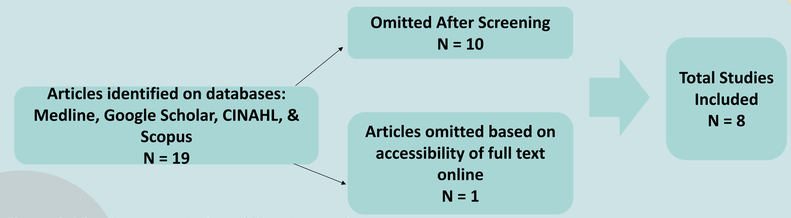

Figure 2. Visual representation of literature review process.

Keywords/Search Queries: "Infants" AND "Obesity OR Weight Gain" AND "antibiotic exposure" AND "gut bacteria"

Inclusion Criteria:	Exclusion Criteria:
Infants 1-23 months of age	Infants over 23 months of age
Articles written in English only	Articles written in foreign languages
Peer-reviewed articles	Congenital illness or malformations

Results

Table 1: Synthesis of main findings from eight pertinent articles used for literature review

Author(s)	Sample	Study Design	Results	Conclusion
Azad, Bridgman, Becker & Kozyrskyj, 2014.[1]	629 children examined at age 9 and 12 in SAGE study	Secondary analysis of provincial health care database in 1995 SAGE cohort study	Antibiotic exposure in the first year of like was more positively associated with the development of overweight in childhood compared to unexposed groups (P= 0.002)	Antibiotic exposure in first year of life significantly increased risk of overweight and central adiposity in boys ages 9 and 12.
Scott et al., 2016.[12]	21714 children in Health Improvement Network (Dataset from UK medical records (1995-2012)	Retrospective cohort study within Health Improvement Network Dataset	Antibiotic exposure associated with increased risk of obesity at 4 years (OR=1.21) Antibiotic exposure within first 2 years of life is associated with 1.2% absolute and 25% relative increase in risk of early childhood obesity	Risk of childhood obesity heightened when 3 or more courses of antibiotics were administered to children under the age of 2.
Turta & Rautava, 2016.[9]	Various studies	Literature review	An outcome of obesity is associated with an increased abundance of phylum Firmucutes and decrease in Bacteriodetes High concentration of intestional bididobacteria may be associated with lower risk of overweight	Prolonged gut microbiota alterations may be the result of repeated antibiotic exposure. Changes in gut microbiota composition associated with development of overweight and obesity.
Edmonson & Eickhoff, 2017.[11]	2-year study involving 607 children (aged 2-71 months) enrolled from 2007-2011	Secondary analysis of data from RCT Intervention for Children with Vesicoureteral Reflux Study	No significant evidence that prolonged exposure to antibiotic TPM/SMX affected weight gain or outcomes of overweight or obesity in healthy infants and young children	The link between prolonged antibiotic use and weight gain remains doubtful. Existing studies lack consistency and precision with respect to many variables: age, sex and antibiotic exposure details, etc.
Mbakwa et al., 2016.[14]	3030 caucasian women pregnant women (34 weeks gestation) recruited Total 979 children were eligible for analysis	Cohort study	β-lactam antibiotics were associated with an increase in weight z-scores during the follow-up period of the study Children exposed to a single course of antibiotics during the first 6 months of life showed an increase in weight gain compared to those who had no exposure. No association between single exposure of antibiotics and obesity between 6-12 months of age	Association to obesity was present after single dose of antibiotics during first 6 months of life.
Shao et al., 2017.[15]	15 cohort studies involving 445 880 participants in developed countries	Systematic review & meta-analysis	Early life antibiotic exposure significantly increased risk of childhood overweight (RR=1.23) and obesity (RR=1.21) and BMI (mean difference: 0.07) 7% increase in risk of overweight (RR = 1.07) and 6& increase in risk for obesity (RR=1.06) with each additional course of antibiotics	Early life antibiotic exposure significantly increased risk of childhood overweight and obesity.
Cox & Blaser, 2015.[16]	Samples from various studies	Literature review	Early life antibiotic exposure can disrupt gut microbiota development and can influence body mass (weight gain or stunted growth) These exposures impact body mass in adulthood	Examining early life characteristics of gut microbiota could shed light on possible interventions directed at mitigating risks associated with obesity.
Pihl et al., 2016.[13]	Samples from various studies	Systematic literature review	Array of factors influence the gut microbiota profile (host genetics, delivery method, diet, age, environment, antibiotics)	Establishment of such factors can provide a basis for obesity prevention initiatives. Understanding the role of gut microbiota is paramount for targeting childhood obesity.

Discussion

All apart from one, studies demonstrated a marked, statistically significant association between early-life antibiotic exposure and the development of overweight or obesity. An increased proportion of Firmicutes to Bacteroidetes is recognized as a marker of obesity.[10] A greater number of courses of antibiotics was associated with a higher risk of developing childhood overweight or obesity. Also, obesity as a result from antibiotic exposure was observed in as little as 6 months from birth. Obesity during childhood can also carry on to adulthood. One study found a relationship between gut microbiota and obesity in only males only.[1] Some mechanisms established in mice models were excessive caloric intake, changes in adiposity, fatty acid metabolism, and regulation of peptide YY and GLP-1 secretion.[17] Multiple factors affect the development of gut microbiota, such as host genetics, delivery method, diet, age, and antibiotic use. Some preventative factors to obesity that have been observed in studies are breastfeeding, healthy diet, and physical activity, however when coupled with antibiotics they had no protective effects.[1] The direct mechanism if the microbiota action on adiposity alterations remain ill-detailed and poorly understood; however, mounting evidence points to the association between altered gut microbiota profiles and increased risk of obesity. Articles also emphasize the increasing need for preventative measures targeting childhood obesity. With a clearer understanding of the role of gut microbiota in the development of childhood obesity can aid in mitigating risks associated with the childhood epidemic.

Limitations:
Variables were adjusted to account for maternal age, pre-gravid BMI, birth weight, sex, delivery mode, etc.[12] Articles also attempted to avoid confounding by excluding smoking pregnant women from secondary analysis.[12]
-Information biases in research where medical records lacked specific information on antibiotic exposure (use, dosage, number of courses, etc.)[11]
- Recall bias was apparent in one study, as prenatal antibiotic use was determined by a questionnaire.[12]
- The nature of the study forced a limited scope of pre-established data in the form of systematic reviews, literature reviews and secondary analyses; performing a randomized-controlled trial which administered antibiotics to humans for the purposes of experimentation is not ethically feasible.

Conclusion

It is presumed that the overprescription of antibiotics and its exposure during infancy significantly contributes to the modern prevalence of obesity due to its potentially harmful effects on the microbiota. However, further studies are needed to confirm these findings in order to establish preventative measures in the future.

Future Directions

To investigate
- the association between antibiotics and the hunger hormone, ghrelin[18,19]
- the association between antibiotics and the satiety hormone leptin[19]
- the implementation of omega-3 fatty acids to combat obesity through the prevention of antibiotic-induced modulation of gut microbiota [20]
- the anti-obesity effects of probiotics (Lactobacillus genus).[21]
- the administration of prebiotics such as FOS, inulin, galacto-oligosaccharides (GOS) and lactulose to prevent and treat childhood obesity.[22]

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