Early Factors Leading to Later Obesity: Interactions of the Microbiome, Epigenome, and Nutrition

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Obesity is a major public health problem in the United States and many other countries. Childhood obesity rates have risen extensively over the last several decades with the numbers continuing to rise. Obese and overweight children are at high risk of becoming overweight adolescents and adults. The causes are multifactorial and are affected by various genetic, behavioral, and environmental factors. This review aims to discuss a previously underrecognized antecedent of obesity and related chronic metabolic diseases such as heart disease and diabetes. Specifically, we highlight the relationship of the microbial ecology of the gastrointestinal tract during early development and the consequent effects on metabolism, epigenetics, and inflammatory responses that can subsequently result in metabolic syndrome. Although studies in this area are just beginning, this area of research is rapidly expanding and may lead to early life interventions that may have significant impacts in the prevention of obesity.

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Introduction

Obesity has become the major personal and public health problem in the United States and is burgeoning in many other countries as well.[1] Some of the urban centers in the most populous country in the world, China, are experiencing a major increase in childhood obesity.[2] Other rapidly developing countries such as Mexico, Brazil, India, and Argentina are also experiencing major increases.[3] Childhood obesity has been associated with the subsequent development of metabolic syndrome in adulthood, which includes obesity, type II diabetes mellitus, hypertension, dyslipidemia, and associated problems (Fig. 1). The long-term implications of this are concerning: the diabetic population in the Indian subcontinent alone is predicted to rise to more than 80 million by the year 2030.[4]

Causes for these increases in obesity are multifactorial and likely have little to do with genetics since these increases are occurring much faster than would be likely with genomic (DNA base pair) alterations. Some of the obvious causes include intakes of more energy than utilized with subsequent storage of the excess energy in the form of fat. Modern lifestyle factors such as lack of exercise, rich foods, and stress unquestionably play major roles. However, many other components have been found to be important in the development of obesity. Early developmental factors are now known to clearly play a role and have been studied by Developmental Origins of Health and Disease (DOHAD); an international society focused on these problems as they relate to early development.

Although storage of excess calories represents one somewhat simplistic mechanism leading to obesity, other factors are involved as well. Our intestinal microbes represent a highly genetically diverse and metabolically active biome that outnumbers our somatic cells and genes by orders of magnitude. They likely play a critical role in altering inflammatory responses, and produce highly bioactive metabolites, some of which may be involved in endocrine and metabolic alterations that may be functional in both infancy and adulthood. In addition, these microbes and their metabolic products may be involved in epigenetic mechanisms that function during critical developmental windows that profoundly affect subsequent phenotypic characteristics including obesity and other health issues during later life.

In this article, we wish to provide a summary of some of the early causes of the adult metabolic diseases, which encompass obesity, type II diabetes, hypertension, and cardiovascular disease. Here we wish to emphasize the relationship of the microbial ecology of the gastrointestinal tract during early development: in the pregnant mother and her fetus, perinatal events that may affect the microbial ecology of the gastrointestinal

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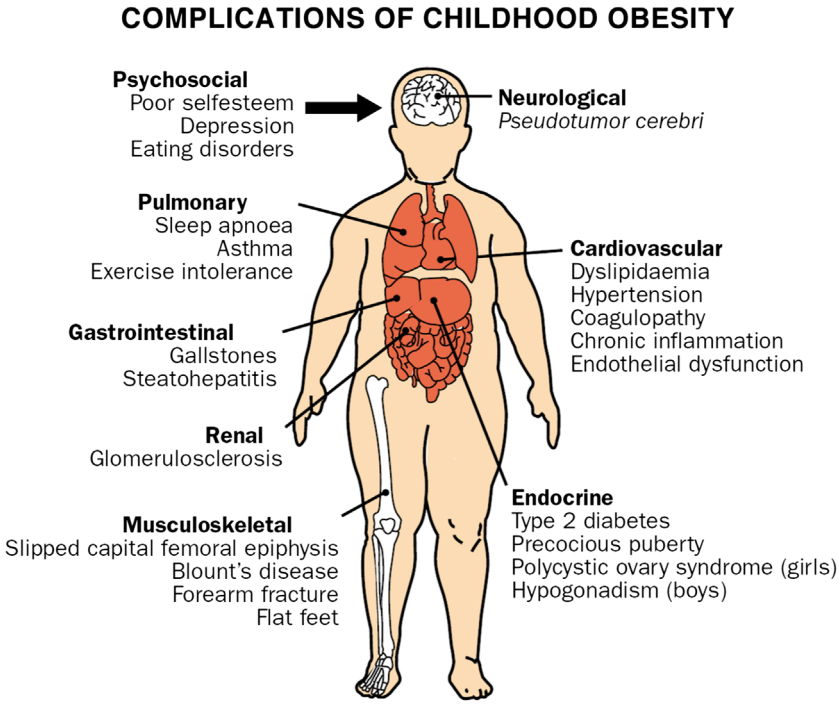

FIG 1. Complications of childhood obesity. (Adapted with permission from Ebbeling et al.[1])

tract of the developing infant, and perturbations during early infancy that alter the intestinal microbiome along with the consequent effects on metabolism, epigenetics, and inflammatory responses that can subsequently result in metabolic syndrome.

The Microbiome in Pregnancy, Peri-Partum, and Early Infancy

Over the past decade, it has become increasingly clear that the microorganisms that are closely associated with human, especially those in our gastrointestinal tracts, harbor a huge ecosystem (the "microbiome") that is highly genetically, transcriptionally, and metabolically active. The major functions of this microbiome involve symbiotic or commensal relationships with their human host. This microbiome interacts closely with a highly immunoreactive intestinal mucosal immune system and has been found to have the capability to pass traits from one generation to the next via maternal contact as well as environmental contact.[5]

The interactions between the microbiome, epigenetic, neuroendocrine, and metabolic systems are likely to play a major role in the genesis of obesity and metabolic syndrome, yet the mechanisms remain poorly delineated. Here we wish to describe some of these relationships and discuss potential pathways that require further study to better understand the actual mechanisms involved.

Here we posit that the early mechanisms leading to obesity may relate to the developing microbiome of the mother and/or fetus before birth. It appears to be dogma that the fetus commonly emerges from a sterile environment and only acquires a relationship with environmental microbes after birth. Under this paradigm, the infant's first stool (meconium) is also sterile. Recent studies contradict this dogma.[5] Microbes have been found to be present in placenta,[6] meconium,[7–9] and amniotic fluid,[10] thus suggesting that there already exists a significant interplay between the environmental microbes and the developing gastrointestinal tract of the fetus prior to delivery. The precise origin of these microbes is not fully understood but studies suggest that the vaginal tract[11] may be one potential source of these microorganisms via ascending transvaginal migration and trans-location through the chorio-decidual membranes. Another mechanism may be through the maternal gastrointestinal tract translocating directly into the maternal blood stream or via cellular transport with transporting cell probably being a form of dendritic cell.[12–14] The fact that microbes found in meconium are closely related to those found in amniotic fluid makes meconium a potentially readily