The role of gut microbiota in human metabolism
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Chapter 1
Introduction

“All disease begins in the gut”
Hippocrates 460BC

The human bowel is home to trillions of bacteria, which outnumber the cells of their host by a factor of ten to one, and collectively their genes outnumber human genes by one hundred-fold. Bacteria colonize the gut soon after birth. Although the initial composition of the gut microbiota varies (1), it becomes relatively stable after the age of 2 years and onward into adult life (2). Together, the gut microbiota functions as an organ, complementing and interacting with human metabolism. Thus, manipulation of the gut microbiota can also have detrimental or therapeutic effects on the human host. In this respect, although fecal microbiota therapy has only recently gained popularity with its success for treating Clostridium difficile infection (3), the use of enterically derived material for treatment of disease goes back as far as the 4th Century BC. During this period Ge Hong, a traditional Chinese medicine doctor, used human fecal suspension given orally to treat food poisoning and severe diarrhea (4). Another Chinese, Li Shizhen, used fermented, fresh, dried or infant feces (for esthetical reasons called “yellow soup”) for the treatment of several gastro-intestinal related illness, including diarrhea (5). The publication by Eiseman et al. in 1958 was the first to report again in the current medical literature on the role of fecal enema’s in the treatment of chronic diarrhea (6). However, understanding the composition and role of specific intestinal organisms in human disease was initially limited by an inability to cultivate most of the microorganisms colonizing the digestive tract. The development of next generation culture-independent tools, such as 16S rRNA gene sequencing (7), have enabled broader insights into the composition of the gut microbiota (8).

As obesity has become an epidemic worldwide, resulting in an increased prevalence of associated disorders such as metabolic syndrome and type 2 diabetes, this thesis has focused on studying the relation between gut microbiota composition and human obesity as well as glucose metabolism. The causes responsible for the development and progression of obesity are complex and involve diverse factors, such as lifestyle habits and genetics. The relationship between the human gut microbiota, obesity
and insulin resistance is reviewed in chapters 2 & 3. Antibiotics disturbing the gut microbiota may predispose patients to develop recurrent Clostridium difficile infections (CDI). There is no evidence-based effective treatment against recurrent CDI, but restoring the gut microbiota seems a logical mechanism to repair the host-defense against CDI. In chapter 4, treatment with infusion of a donor feces solution was compared to vancomycin in patients with recurrent CDI.

Although convincing in mouse models, it remains difficult to conclude whether disturbances in gut microbiota are cause or just consequence of obesity in humans. Particularly given the fact that environmental confounding factors, notably dietary changes, are known to have a role both in the modulation of the microbiota and the development of obesity. Taking a reductionist approach as used in chapter 4, restoration of a ‘lean’ gut microbiota may ameliorate obesity and its associated diseases. In chapter 5 we examined this hypothesis by infusion of lean donor feces in participants with metabolic syndrome. In this double-blind randomised controlled trial we investigated the effect of donor feces transplantation on insulin sensitivity.

Since treatment with oral medication has been described to alter gut microbiota, we decided to investigate the effect of short-term oral antibiotics (chapter 6) on gut microbiota composition, bile acid metabolism and insulin sensitivity.

Finally, inflammation of visceral fat plays a key role in the development of insulin resistance and subsequent type 2 diabetes, yet the pathophysiological trigger for this chronic inflammation remains poorly understood. In chapter 7 we examined whether the gut microbiota composition plays a role in the inflammation of visceral adipose tissue.

In chapter 8 we reviewed the role of fecal transplant in clinical practice as well as its potential pitfalls.

Chapter 9 summarises the most important findings of this thesis and advises on future directions. Chapter 10 is the Dutch-language summary.
References