

**Modulation of the Gut Microbiome –
from Phenomenology to Health Claims
and Dietary Recommendations
to tackle obesity**

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Obesity Epidemic

In the WHO/European Region



over 50%
of people are
overweight or **obese**



over 20%
of people are
obese

www.euro.who.int/obesity

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Obesity Epidemic

- Given the current epidemic of obesity and T2DM , novel treatment options are urgently warranted.
 - Prebiotic fibers
 - Modulation of the microbiome – relation to insulin resistance

Obesity and Gut Microbiota

- The gut microbiota has received much attention because of its association with obesity and T2DM, although **causality** remains to be proven.

Unfortunately

- Contrasting data, esp. pertaining to composition microbiota
- Many studies have been carried out in rodents that have a markedly different gut microbiota and (innate) immune system,
- Underscoring that murine causation studies may, but do not necessarily equate to human causation regarding metabolic microbiota in metabolism.

Current status

- “Convincing” evidence for a potential causal role of microbiota in diverse diseases including obesity and type II diabetes

Evidence (animal)

Feces transplantation from obese mice in lean germ-free recipient mice on high fat diet:

- High increase weight recipient mice, normally resistant to high-fat diets.

Feces transplantation from lean mice in obese recipient mice on high fat diet:

- Weight loss without affecting food intake – suggestive of increased energy dissipation.

Evidence (animal)

- Transfer of human feces from twin pairs discordant for obesity into GF mice induced more weight gain after FMT of feces from the obese co-twin compared with feces from the lean co-twin.

Ridaura et al. Science 2013:341

Transfer of Intestinal Microbiota From Lean Donors to Individuals With Metabolic Syndrome

- ↑ Insulin Sensitivity
- ↑ levels of butyrate-producing intestinal microbiota

Vrieze et al. Gastroenterology. 2012 Oct;143(4)

Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome

- Lean donor FMT in obese metabolic syndrome patients improves insulin sensitivity
- Beneficial effects of lean donor FMT are transient
- Improvement in insulin sensitivity is linked to changes in plasma metabolites
- Response to lean donor FMT is driven by baseline fecal microbiota composition – less diverse → ↑ response

Changes in microbiota overweight/diabetes

- Less diversity
- Decreased occurrence butyrate-producing bacteria, e.g. *Faecalibacterium prausnitzii*
- Increase of mucin-degrading bacteria, esp. *Akkermansia*

- Changes in ratio Firmicutes/Bacteroidetes, associated with insulin resistance (measured as FG and HbA1c).
- Limitation – low reproducibility of human studies

Modulation Microbiome

Possible Mechanisms of Action

- Composition
- Metabolites/SCFAs
- Altering physiochemical properties of endogenous metabolites (bile acids – energy metabolism)

Modulation of Microbiome – Physiological effect?

- Merely reporting of associations intestinal microbial composition & metabolic disorders like obesity and type 2 diabetes
- No causal relationship established

Cause and Effect?

- How gut microorganisms interact with the host is still largely enigmatic
- Multiple pathways may be involved.

Health claims - EFSA

EFSA Health claim: primary requirements:

- Claimed effect beneficial to human health (physiologically beneficial effect)?
- Food constituent sufficiently described?
- Cause and effect relationship established?

Pre-requisite for health claim substantiation

- Cause and effect relationship established!
- Set-back microbiome studies: status quo at follow-up often not sufficiently distinctive, only descriptive.

Microbiota – study design

- Kinetics of responses:
 - Kinetic changes in microbiota composition, combined with
 - Kinetic changes in –omics parameters

vs.

- kinetic changes in physiological parameters

Take home

The intestinal microbiota has been implicated in a range of metabolic disorders, but **causal findings** have so far been lacking.

Clue of kinetics

From phenomenology to cause and effect

Opens up the road to microbiota-related health claims and dietary recommendation



Thank you!

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