Pro- and prebiotics as modulators of gut microbiome in management of obesity and metabolic diseases

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Characteristics of the human GI tract and Microbiota

More than a 100 trillion microbes, more than 1000 different species

At least 100 x as many genes as average human

Microbial population change throughout the GI tract

Unlike human genes, GI microbes can be altered by drugs, diet, other.

Opportunity to improve health with probiotics and prebiotics

Source: Krogius-Kurikka, 2011, Lower Gastrointestinal Microbiota in Health and Irritable Bowel Syndrome: Characterisation and Effect of Probiotic Intervention, University of Helsinki

Human Microbiome Project Consortium Nature 2012
Richness of human gut microbiome correlates with metabolic markers

doi:10.1038/nature12506

Figure 1 | Distribution of low and high gene count individuals (n = 292).

Le Chaletier et al & MetaHit 2013
A metagenome-wide association study of gut microbiota in type 2 diabetes

doi:10.1038/nature11450

Qin et al & MetaHit 2012
Gut microbiota affects body weight and insulin sensitivity

Turnbaugh et al. 2006

Vrieze et al. 2012
Focus on bifidobacteria:
*Reduced bifidobacteria in obesity*

<table>
<thead>
<tr>
<th>Group by genus</th>
<th>Study (year)</th>
<th>Sample size</th>
<th>SDM and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obese</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Collado <em>et al.</em> (2008)</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Kalliomäki <em>et al.</em> (2008)</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Schwiertz <em>et al.</em> (2009)</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Balamurugan <em>et al.</em> (2010)</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Santacruz <em>et al.</em> (2010)</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Zuo <em>et al.</em> (2011)</td>
<td>52</td>
<td>52</td>
</tr>
</tbody>
</table>

*Bifidobacterium* (log copies DNA/ml)

Angelakis *et al.* 2012
Intestinal health contributes to metabolic disease

High fat diet
Life-style

Increased intestinal permeability

Microbial components (LPS) entering the circulation

Tissue inflammation

Insulin resistance

Metabolic syndrome, Type 2 diabetes

Can this be interfered?
**Bifidobacterium animalis** ssp. *lactis* 420 (B420) in prevention and treatment of obesity and diabetes

**Obesity**

- High-fat diet (60 E%)

**Control or high-fat diet (Research Diets)**

- *B. lactis* 420: $10^9$ cfu or vehicle (gavage)

**Diabetes**

- Extremely high-fat diet (72 E%), carbohydrate-free

**Chow or high fat, carbohydrate-free diet**

- *B. lactis* 420: $10^8, 10^9, 10^{10}$ cfu or vehicle

4 weeks
Obesity model

B420 ameliorates weight gain

Evolution Body weight gain

Stenman et al. 2014
Diabetes model

**Insulin sensitivity**

Glucose turnover rate, mg/kg.min

- NC
- V
- B 420

High fat, low carb diet

Amar et al. 2011

**Plasma LPS (EU/ml)**

- NC
- Control
- B420

High fat, low carb diet

Stenman et al. 2014
Cell Metabolism

The Gut Microbiota Regulates Intestinal CD4 T Cells Expressing RORγt and Controls Metabolic Disease

Garioud et al., Cell Metabol 2015
Gut microorganisms as promising targets for the management of type 2 diabetes

Delzenne et al. 2015
Probiotic Supplementation Attenuates Increases in Body Mass and Fat Mass During High-Fat Diet in Healthy Young Adults

- 20 non-obese male volunteers challenged with high-fat, high-energy diet for 4 weeks
- 8-strain probiotic combination reduced body mass gain and fat mass gain during high fat diet
Intake of *Lactobacillus reuteri* Improves Incretin and Insulin Secretion in Glucose-Tolerant Humans: A Proof of Concept

- 21 adult volunteers treated for 4 wks
- *L. reuteri* modified *insulin and increting response to glucose*
Effect of *Lactobacillus rhamnosus* CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women

- 125 adult volunteers treated for 24 wks with *L. rhamnosus* + 0.3g prebiotic or placebo (12 weeks energy restriction)
- Overall no differences, but *improved weight loss in women* with probiotics

Dietary modulation of the gut microbiota – a randomised controlled trial in obese postmenopausal women

- 58 post-menopausal women treated for 6 wks with *L. paracasei*, flaxseed mucilage or placebo
- *Prebiotic treatment improved insulin sensitivity*
The effect of separate or combined supplementation of B420 and Litesse Polydextrose on body fat mass

- Randomized, double-blind, parallel design
- Study design and execution follows GCP guidelines
- N = 58 per arm, 232 in total (225 recruited in total)
- Overweight and obese individuals
- Primary outcome: **Body fat mass** (by DEXA)

| Control: microcrystalline cellulose (MCC) | 6 months + follow-up |
| Probiotic: B420 + MCC ($10^{10}$ CFU) |
| Prebiotic: Litesse® polydextrose (12g) |
| Synbiotic: Litesse® + B420 |

Baseline

**ClinicalTrials.gov** NCT01978691
Microbiome research is revealing new exciting interactions between microbes and health, particularly in relation to metabolic health.

Probiotics and prebiotics provide an opportunity to modify gut microbiota and homeostasis at gut epithelial level, with potential to improve metabolic health.

Pre-clinical data on probiotics, prebiotics and their combinations is promising and warrants clinical research.

Current clinical evidence shows promise but larger and higher quality trials are needed:

- Clear need to identify the most effective candidates
- Effects in humans appear to be modest, but meaningful
Thank you!

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