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Antibiotic-Exposed Donor Microbiota and Weight Gain After Fecal Transplantation

1. Overview and Key Conclusion

The strongest causal evidence that antibiotic-exposed donor microbiota can induce weight gain in recipients comes from controlled murine studies using germ-free mice. These studies demonstrate that microbiota shaped by early-life, low-dose antibiotic exposure can transmit increased adiposity when transplanted into antibiotic-naïve recipients. Comparable, well-controlled human fecal microbiota transplantation (FMT) studies demonstrating the same effect do not currently exist.

2. Landmark Donor-to-Recipient Transfer Study

Cox et al., Cell (2014)

Study Design

- Donor mice were exposed to low-dose penicillin (LDP) early in life.
- Cecal microbiota from adult LDP-exposed donors were transplanted into germ-free recipient mice.
- Recipient mice were not exposed to antibiotics, isolating microbiota-mediated effects.

Key Quantitative Outcomes

- Increased total mass gain rate: +0.078 g/day compared with controls ($p = 0.01$)
- Increased fat mass gain rate: +0.058 g/day compared with controls ($p = 0.0012$)
- No significant change in lean mass

Interpretation

- The phenotype was driven by microbial community composition rather than direct antibiotic toxicity.
- Increased adiposity occurred without increased lean tissue, indicating altered energy storage rather than generalized growth.

3. Microbiota Stability and Serial Transfer Effects

- A second transfer (recipient to new germ-free mice) abolished the adiposity phenotype.
- This indicates that the obesogenic microbiota configuration may be ecologically unstable without ongoing antibiotic selection pressure.
- The effect appears strongest when microbiota are transferred soon after antibiotic-driven selection.

4. Supporting Evidence from Antibiotic Exposure Studies

Cho et al., Nature (2012)

Key Findings

- Early-life, low-dose antibiotic exposure increased fat mass in mice.
- Altered metabolic hormone signaling was observed, including elevated glucose-dependent insulinotropic polypeptide (GIP).
- Example: GIP levels approximately 39.1 ± 2.5 pg/mL in antibiotic-exposed mice versus 24.4 ± 4.2 pg/mL in controls.

Relevance

- This work established antibiotics as drivers of long-term metabolic programming.
- While not focused primarily on fecal transfer, it supports the mechanistic plausibility observed in later transplant studies.

5. Mechanistic Interpretation

Microbiota-Mediated Effects

- Transplant experiments demonstrate causality independent of antibiotic exposure in recipients.
- Changes likely involve altered energy harvest, bile acid metabolism, short-chain fatty acid signaling, and incretin hormone modulation.
- Preferential increase in fat mass suggests metabolic reprogramming rather than enhanced growth.
- Loss of effect after serial transfer suggests reliance on antibiotic-shaped ecological niches that may normalize over time.

6. Human Evidence and Limitations

- No high-quality human FMT trials currently demonstrate weight gain attributable specifically to antibiotic-exposed donors.
- Human data consist primarily of observational associations between antibiotic exposure and later obesity risk.
- Differences in diet, baseline microbiota, host physiology, and FMT practices limit direct extrapolation from animal models.

7. Practical Takeaways

- Antibiotic-exposed donor microbiota can causally induce fat gain in germ-free mice.
- Effects are strongest with early-life exposure and recent microbiota selection.
- Phenotype stability appears limited without continued selective pressure.
- Human relevance remains plausible but unproven by direct donor-to-recipient FMT studies.