Roux-en-Y Gastric Bypass and Sleeve Gastrectomy Induce Substantial And Persistent Changes In Microbial Communities and Metabolic Pathways

PRESENTER: **Jerry T. Dang**

CO-AUTHORS: Valentin Mocanu, Heekuk Park, Michael Laffin, Naomi Hotte, Shahzeer Karmali, Karen Madsen, Daniel W. Birch

Department of Surgery, University of Alberta, Edmonton, Alberta, Canada

BACKGROUND

- Bariatric surgery induces significant microbial and metabolomic changes, however, links between microbial and metabolic pathways have not been fully elucidated
- The objective of this study was to conduct a comprehensive investigation of the microbial, metabolomic, and inflammatory changes that occur following Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).

METHODS

- A prospective clinical trial was conducted with 80 participants undergoing RYGB, SG, and non-operative controls
- Clinical parameters, blood samples, and fecal samples were collected pre-intervention and at three and nine months
- Multi-omics approach was used to perform integrated microbial-metabolomic analysis to identify functional pathways in which weight loss and metabolic changes occur after surgery.

KEY RESULTS

- RYGB led to profound microbial changes including reductions in alpha-diversity and numerous changes at the genus level
- Associated with a reduction in inflammation and significant weight loss. Reduction in Romboutsia genera correlated strongly with weight loss and its obliteration correlated with improved weight loss and insulin resistance, possibly through decreases in glycerophospholipids
- SG associated with a decrease in a cluster of Firmicutes genera including Butyriciccocus, Eubacterium ventriosum and Monoglobus, which correlated with decreased weight, insulin resistance, and systemic inflammation mediated through the aminoacyl-tRNA biosynthesis pathway

Comprehensive microbial-metabolomic analysis identified three unique pathways in which RYGB and SG induce weight loss, improve glucose metabolism and decrease systemic inflammation

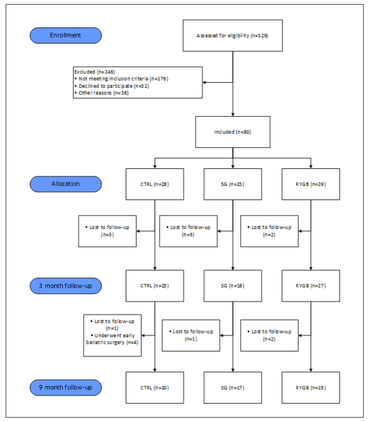


Figure 1. STROBE flow chart for observational studies

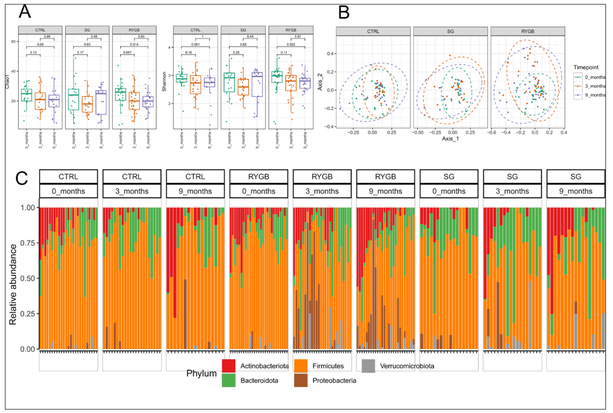


Figure 2. Differences in relative microbial abundance between non-operative control, sleeve gastrectomy and Roux-en-Y gastric bypass 0, 3 and 9 months. (A) Between timepoint differences in α diversity using the Chao1 and Shannon indices. (B) Between timepoint differences in β diversity using the Bray-Curtis dissimilarity index. (C) Taxa bar plots demonstrating phylum level differences in relative microbial abundance between groups.

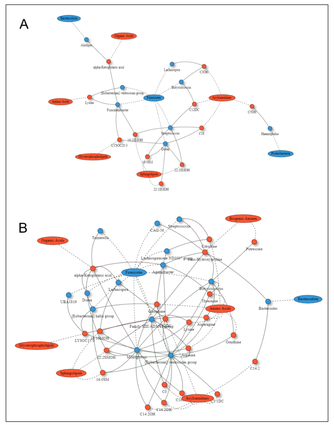


Figure 3. Network plot of Spearman correlations between differential microbes and metabolites at 3 and 9 months compared to baseline for sleeve gastrectomy. Metabolites are represented as red circles and metabolite classes as red ovals. Microbial genera are represented as blue circles and phyla as blue ovals. Positive and negative correlations are indicated using red and green colors, respectively. SM, sphingomyelins; SMOH, hydroxysphingomyelin; PC, phosphatidylcholine; LYSOC, lysophosphatidylcholine; C, carnitines.

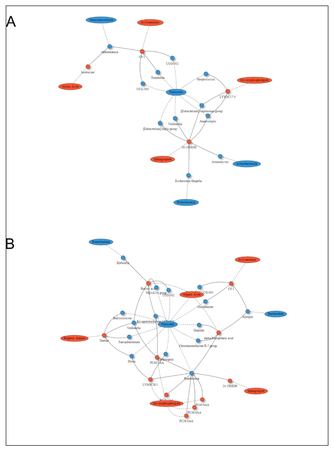


Figure 4. Network plot of Spearman correlations between differential microbes and metabolites at 3 and 9 months compared to baseline for Roux-en-Y gastric bypass. Metabolites are represented as red circles and metabolite classes as red ovals. Microbial genera are represented as blue circles and phyla as blue ovals. Positive and negative correlations are indicated using red and green colors, respectively. SM, sphingomyelins; SMOH, hydroxysphingomyelin; PC, phosphatidylcholine; LYSOC, lysophosphatidylcholine; C, carnitines.

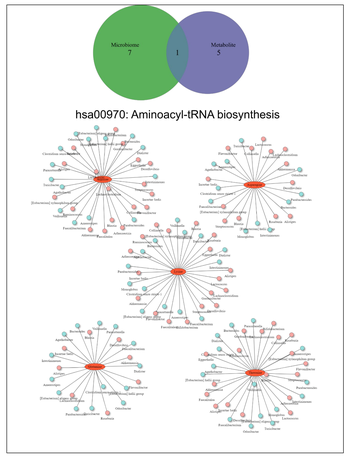


Figure 7. Venn diagram of significant differential pathways in functional network analysis implemented with the KEGG metabolic pathway database. Interaction network plots of enriched amino acids in the aminoacyl-transfer-RNA biosynthesis pathway with microbes that participate in its metabolism. Red colors indicate significantly up-regulated metabolites or microbes, while blue colors indicate significantly down-regulated metabolites or microbes.

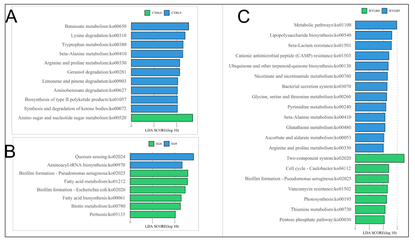


Figure 5. Microbial functional prediction of KEGG-based KO functions using linear discriminant analysis comparing 9 months to baseline for (A) non-operative control, (B) sleeve gastrectomy, and (C) Roux-en-Y gastric bypass. Green represents enriched pathways at baseline and blue represents enriched pathways at 9 months. P-value < 0.05 is considered statistically significant.

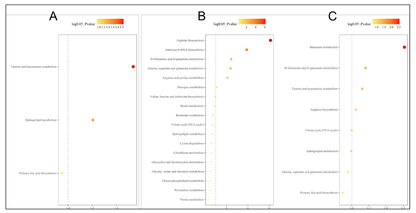


Figure 6. Differential metabolic pathway enrichment analysis comparing 9 months to baseline for (A) non-operative control, (B) sleeve gastrectomy, and (C) Roux-en-Y gastric bypass. P-value < 0.05 (or log0.05 p-value > 1.0) is considered statistically significant.

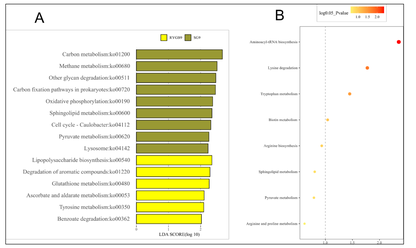


Figure 8. Functional analysis between sleeve gastrectomy and Roux-en-Y gastric bypass at 9 months for (A) microbial pathways and (B) metabolomic pathways. Bright yellow represents enriched pathways for Roux-en-Y gastric bypass and dark yellow represents enriched pathways for sleeve gastrectomy. P-value < 0.05 (or log0.05 p-value > 1.0) is considered statistically significant.

DISCUSSION

- RYGB was associated with decreases in the abundance of Romboutsia which correlated to decreases in glycerophospholipids as well as lower weight and insulin resistance. Glycerophospholipids are a group of molecules involved in obesity and insulin resistance
- SG demonstrated a unique pathway linked to the decreased abundance of a cluster of three Firmicutes bacteria. This Firmicutes shift was correlated with an increase in five amino acids which consequently enriched an important protein biosynthesis pathway, the aminoacyl-tRNA pathway. The loss of this cluster also correlated with decreased weight, insulin resistance, and systemic inflammation.
- When performing between group comparisons, SG demonstrated an enriched pathway at 9 months compared to RYGB. The sphingolipid metabolism pathway was enriched due to the loss of a cluster of five Firmicutes bacteria which correlated to increases in sphingomyelins and hydroxysphingomyelins. Depletion of sphingolipids has been associated with the development of diabetes and impaired pancreatic β-cell function. In our study, these changes were linked to improved glucose tolerance.

CONCLUSIONS

- This comprehensive microbial-metabolomic analysis of bariatric surgery identified potential pathways in which interactions between gut microbiota and metabolites potentiate effects on weight, glucose metabolism, and systemic inflammation.

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