Ascending and Descending Colon Tissue Metabolite Differences of Healthy Adults Across BMI Classes

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Purpose of Study:

Obesity is an established risk factor for development of colorectal cancer (CRC) via metabolic reprogramming of normal colonic metabolism and inflammation. Few studies have examined the colon tissue metabolism of healthy adults and metabolic profile distinctions between ascending and descending colon with changes to body mass index (BMI). In this study, we employed non-targeted metabolomics as a sensitive technique to explore the variation in metabolite profiles across a suite of chemical classes. Metabolite distinctions in respective ascending and descending colon tissue among normal weight (NW), overweight (OW), and obese (OB) adults merits attention to reduce CRC risk.

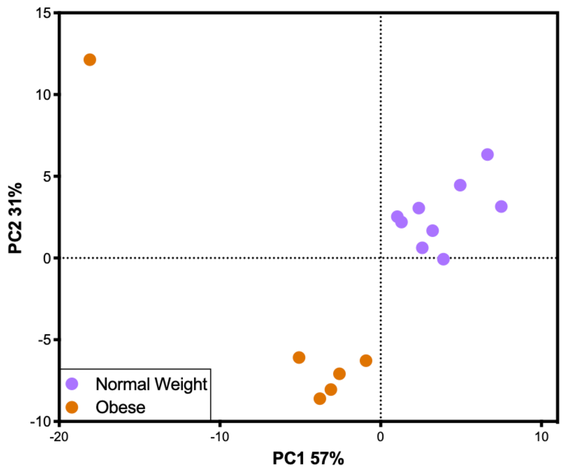

Figure 3: PLS-DA of Normal vs Obese individuals' descending colon

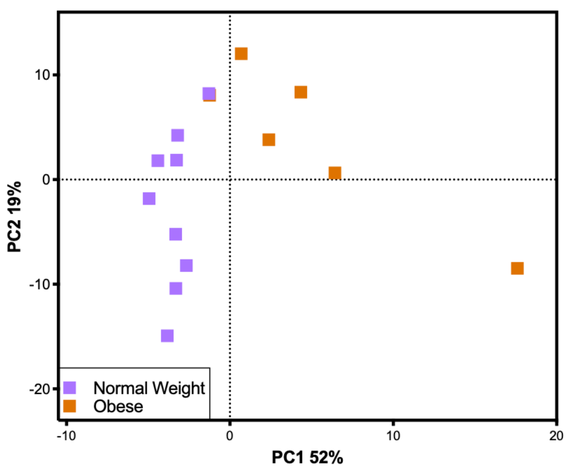

Figure 4: PLS-DA of Normal vs Obese individuals' ascending colon

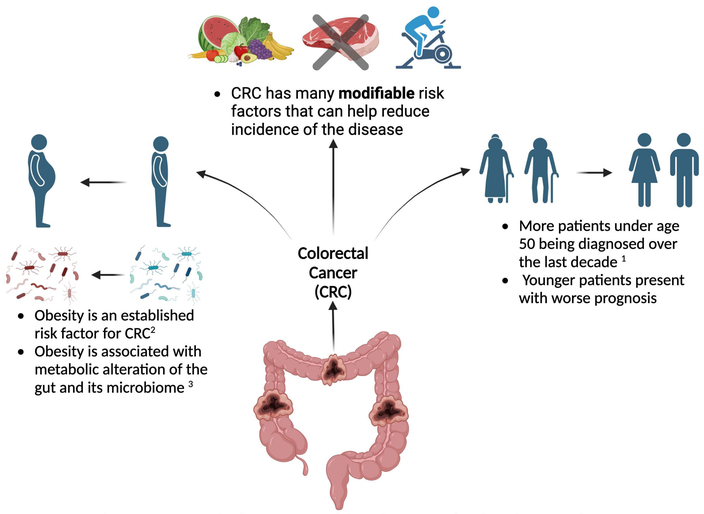

Figure 1: Risk factors and background of colorectal cancer

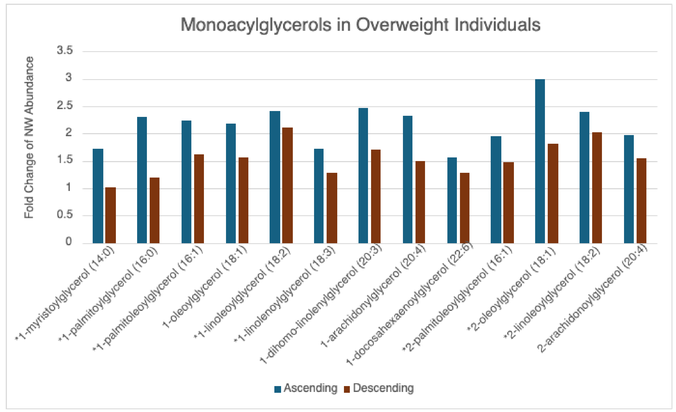

Figure 5: Graph showing fold change of monacylglycerols on each colon side of OW compared to the mean level of respective metabolites in the NW group. (*) indicates significance ($p<0.05$) in the ascending colon. No monoacylglycerols levels were significant in the descending colon.

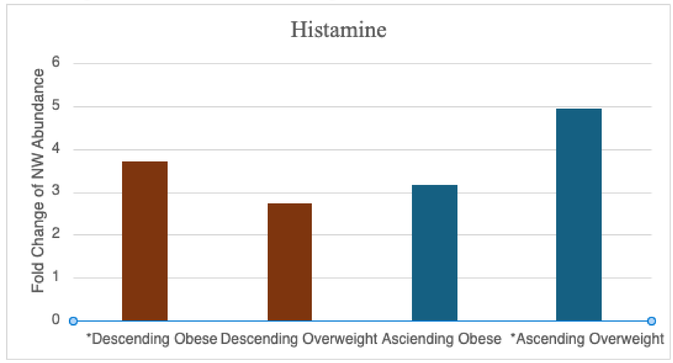

Figure 6: Graph showing the fold change of histamine in OW and OB groups compared to the mean abundance level in NW. (*) indicates significance ($p<0.05$)

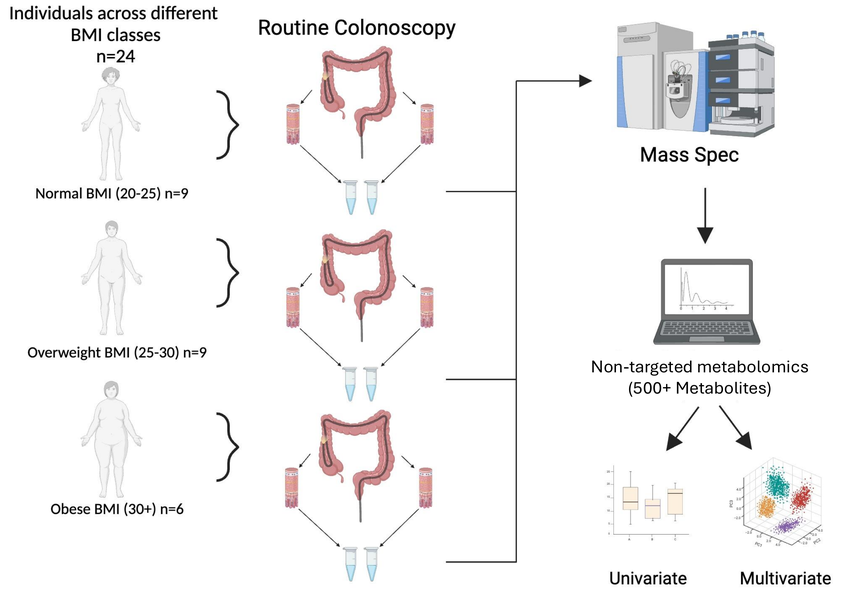

Figure 2: Study design and methods. This study is a secondary analysis from the data of Baxter et al. in 2020.

Summary of Results:

PLS-DA revealed distinct separation in metabolite profiles in ascending and descending tissues among different BMI groups. A total of 61 metabolites were significantly different in OW and OB compared to NW (OB=13, OW=48). In the descending colon, 57 metabolites were significantly different in NW compared to OB and OW (OB=7, OW=50). Histamine was one of the top 5 difference driving metabolites of the NW vs. OB comparison, due to its increase in the OB group. This increase was significant in the descending colon ($p<0.05$) and near significance in the ascending colon ($0.05<p<0.10$). Histamine was also elevated in the ascending colon of OW individuals. Multiple monoacylglycerols had significant increases in only the ascending colon of OW compared to NW.

Conclusions & Future Considerations:

- The metabolic profile of the **ascending colon** differs between BMI classes.
- The metabolic profile of the **descending colon** differs between BMI classes.
- Elevated histamine levels in obese individuals' colon provides evidence for chronic low grade gut inflammation seen in obesity.
- Monoacylglycerol elevation in overweight individuals' ascending colon may contribute to fat storage metabolism and altered endocannabinoid signaling.
- Datasets of healthy adult colon metabolite signatures could become biomarkers of metabolic reprogramming during weight management and for reduced inflammation in control and prevention of CRC.
- Future studies with a diet-controlled intervention prior to colonoscopy could inform more targeted metabolite analysis

Acknowledgements

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References: 1. Virostko J, Capasso A, Yankeelov TE, Goodgame B. Recent trends in the age at diagnosis of colorectal cancer in the US National Cancer Data Base, 2004-2015. *Cancer*. 2019;125(21):3828-3835. doi:https://doi.org/10.1002/cncr.32347, 2. Zeng H, Lazarova DL. Obesity-related colon cancer: Dietary factors and their mechanisms of anticancer action‡. *Clinical and Experimental Pharmacology and Physiology*. 2012;39(2):161-167. doi:https://doi.org/10.1111/j.1440-1681.2011.0558.x, 3. Zivana Puljiz, Marko Kumric, Josip Vrdoljak, et al. Obesity, Gut Microbiota, and Metabolome: From Pathophysiology to Nutritional Interventions. *Nutrients*. 2023;15(10):2236-2236. doi:https://doi.org/10.3390/nu15102236, 4. Baxter BA, Parker KD, Nosler MJ, et al. Metabolite profile comparisons between ascending and descending colon tissue in healthy adults. *World Journal of Gastroenterology*. 2020;26(3):335-352. doi:10.3748/wjg.v26.i3.335