The Wondrous Gut: From the Microbiome to Bariatric Surgery

An Inside Story

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To my knowledge, I have no conflicts of interest related to this presentation...

Pharmacist Objectives

Discuss the microbiota within the human gut with regard to its acquisition and role
Describe the impact of an imbalance in the gut microbiome and links to disorders such as obesity, metabolic syndrome, irritable bowel syndrome, and mental disorders
Review non-pharmacological and pharmacological therapies to help restore balance to the gut microbiome
Discuss the current data related to obesity in the United States and the history of bariatric procedures
Review the most popular surgical options available and the requirements that may need to be met by the candidate
Identify medication considerations and nutritional insufficiencies post-surgery on which a pharmacist could intervene
Discuss barriers to the long-term weight loss success of the patient
### Technician Objectives

- Discuss the microbiota within the human gut with regard to its acquisition and role
- Understand the impact of an imbalance in the gut microbiome and links to disorders such as obesity, metabolic syndrome, irritable bowel syndrome, and mental disorders
- Review the current data related to obesity in the United States and the history of bariatric procedures
- Review the most popular surgical options available and the requirements that may need to be met by the candidate
- Identify medication considerations, nutritional insufficiencies, and side effects post-surgery
- Discuss barriers to the long-term weight loss success of the patient

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### Microbiome

> “The ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space.”

Dr. Joshua Lederberg, American Molecular Biologist, Nobel Prize Winner
Research

"I then most always saw, with great wonder, that in the said matter there were many very little living animalculs, very prettily a-moving."—Antonie van Leeuwenhoek (1632–1723)

In 2007, US National Institutes of Health funded a research initiative in order to increase knowledge of how microbial flora affect our overall health and disease.

Are They Equal?

**MICROBIOME**
Environment in which the consolidated genomes of microorganisms exist

**MICROBIOTA**
Individual groups of microorganisms
- Bacteria
- Fungi
- Protozoa
- Viruses

MICROBIOME

MICROBIOTA
Fun Facts

- Is variable from individual to individual
- Each of us has our own microbial “fingerprint”
- Microbial cells have a mass of > 1.2kg
  - 1kg = nose
  - 20g = mouth
  - 20g = vagina
  - 200g = skin

Kissing for 10 seconds transfers @ 80 million bacteria
Couples reporting they kiss often have more similar microbiota than those that do not

Factors Affecting Our Initial Microbiome

- Gained from the mother in utero
  - Antibiotic use during pregnancy
- Mode of delivery matters!
  - Vaginal delivery
  - Caesarean delivery
- Infant diet
  - Breast milk
  - Formula

Role of the Gut Microbiome

- Digestion
- Metabolism of nutrients
- Assist with vitamin production
- Immune system development
- Maintaining the integrity of a barrier within the gut
- Mediating communication between the gut and brain

Drug Metabolism – Part of the Job!

Metabolic Activities
Gut Dysbiosis = Microbial Imbalance
Permeability of intestines increased
Promotes translocation of bacteria
Endotoxemia
Inflammation
Dysfunction of immune response
Decreased gastric acid secretion and GI motility
Decreased bile acids in the colon

Correlations With Disease States
Irritable bowel syndrome (IBS)
Mental Disorders
Metabolic syndrome
Obesity

Irritable Bowel Syndrome (IBS)
Diversity of stool microbiome components drastically decreased
- Bifidobacterium
- Lactobacillus
- Faecalibacterium prausnitzii
Alteration results in IBS symptoms
- Motility
- Permeability
- Visceral perception
- Food processing
Mental Disorders

Gut Microbiome

- Anxiety
- Depression
- Stress
- Autism

Gut-Brain Axis

Bi-directional pathway through which the central nervous system and the gut communicate

Antibiotic therapy and diet – potentially affect brain function by shaping the microbiome components

Factors contributing to dysbiosis of the gut:
- Smoking
- Alcohol

Metabolic Syndrome

Diagnosis consisting of 3 or more criteria:
- Insulin resistance
- Obesity
- Dyslipidemia
- Hypertension

Disruption of the equilibrium between the immune system and the gut microbes may result in a transfer of bacterial particles and progression of "metabolic endotoxemia". This leads to systemic inflammation.
Obesity

Obesity microbiome:
- Bacteroidetes phylum – Decreased
- Firmicutes phylum – Increased

Weight gain:
Fasting induced adiposity factor (Fiaf) – can be suppressed by microbiota and decrease triglyceride metabolism
Lipopolysaccharides (LPS) – produced by gram negative bacteria


Nonpharmacological

REDUCE HARMFUL ORGANISMS

Polyphenol rich foods:
- Vegetables
- Fruits
- Nuts/seeds
- Wine
- Cocoa products

Limit consumption of:
- Animal protein
- Saturated fat
- Overall total fat < 30% of intake

IMPROVE MICROBIAL DIVERSITY

Increase exercise
Increase protein intake
High fiber intake

Pharmacological Options

PREBIOTICS

Non-digestible oligosaccharides
Promote proliferation of colonic lactobacilli and bifidobacteria
Result: possible improvement of a microbiome supporting weight loss
Adverse effect: gas/bloating
Natural examples: tomatoes, berries, bananas, legumes, flax seed

PROBIOTICS

Touted to protect host from pathogenic microbes and yeast overgrowth
Result: possible improvement of a microbiome supporting weight loss
Adverse effect: gas/bloating
Natural examples: yogurt, sauerkraut, kimchi, miso soup

**Eubiotic - Xifaxin® (rifaximin)**

**Indications**
- Hepatic encephalopathy: 550mg twice daily
- Irritable bowel syndrome WITH diarrhea: 550mg three times daily X 3-4 days
- Traveler's diarrhea – non invasive E. coli: 200mg three times daily X 3 days

**Off use:** 2nd or subsequent recurrence of C. diff infection – 400mg three times daily for 20 days

Metabolized by CYP3A
Excreted 96.6% unchanged in feces


**Fecal Microbiota Transplantation (FMT)**

Used as early as 4th century China

Now utilized in treatment of:
- *C. Difficile* infections
- Inflammatory bowel disease
- Metabolic syndrome/Obesity
- Possible positive impact on psychiatric issues – depression

**Procedure:**
- Procure donor screened for pathogens and family history of autoimmune, malignant, and metabolic diseases
- Mix feces with normal saline or water then filter
- Administer through colonoscopy, retention enema, nasogastric tube, nasojejunal tube


**Biome Testing**

“The world’s first sequencing based microbiome test.”

Provide a stool sample for testing. Receive a report with information about which microbes may be affecting your health.

Possibly covered by insurance under “out of network” provider if ordered by provider.
Bariatric Solutions and Considerations

Hazards of Obesity

- Morbidity ↑ with BMI > 20
- Chronic pain ↑ by 2 to 4x
- Higher probability of cancers
- Risk of Type II Diabetes and Coronary Heart Disease at BMI > 22
- Mental health issues

- Mortality ↑ with BMI > 25
- Sleep apnea
- Lipid levels ↑ with BMI > 25
- Congestive Heart Failure
- Stroke risk

Obesity Related Healthcare Costs for Preventable Disease

- Obesity is a leading factor in healthcare costs.
- Nationally, nearly 21% of annual medical spending is linked to obesity.
- Rising costs: $190.2 billion!
Obesity Statistics

Bariatric Surgery

Impact to Health

- Type II Diabetes – positive outcome in 90% of patients
- Female’s ability to conceive improves
- Overall improvement in quality of life
- Decrease in hypertension and dyslipidemia resulting in lowering doses or medication discontinuation
- Self-esteem affected
Most Popular Procedures

Estimate of Bariatric Surgery Numbers, 2011-2017

Surgical Procedures

- Restrictive
  - Decrease stomach capacity
  - Result: Intake of calories decreased

- Malabsorptive
  - Trim the length of the small intestine
  - Result: Nutrient absorption affected

- Combined
  - Decrease stomach size and length of small intestine

Laparoscopic Adjustable Gastric Band

The EMA's total bariatric procedure numbers are based on the best estimates from available data (ICD‐10‐CM, NRBQIP, National Hospital Services (Interim unpublished estimates)).
### Pros/Cons

**PRO**
- 40 to 50% loss of weight
- Decreased capacity of stomach
- Reversible – no rerouting or removal
- Lowest rate of immediate post-op issues
- Shorter hospital stay – outpatient
- Less vitamin/mineral deficiencies

**CON**
- Slower weight loss rate
- Higher incidence of patients not losing > 50%
- Foreign device implanted
- Mechanical issues
- Has the highest incidence of revision surgeries

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### Gastric Bypass (Roux-en-Y)

**PRO**
- 60 to 80% loss of weight
- Decreased ability to ingest food – overeat
- Increased physical activity
- Positive impact on gut hormones
- Patients typically maintain 50% weight loss

**CON**
- Higher risk of complication
- Vitamin deficiencies: lifelong supplementation
- Longer hospital stay
- Irreversible
**Sleeve Gastrectomy (SG or VSG)**

**PROS**
- Capacity of stomach decreased
- Weight loss of > 50%
- No rerouting
- Typically a 2 day stay inpatient
- Positive impact on gut hormones

**CONS**
- Irreversible
- Long term deficiencies of vitamins
- Increased possibility of early complications

**Duodenal Switch**
*(Biliopancreatic diversion with duodenal switch)*
Pros/Cons

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the greatest weight loss potential</td>
<td>Highest rate of complications</td>
</tr>
<tr>
<td>“Normal” meals – at a later time</td>
<td>Lengthier inpatient stay</td>
</tr>
<tr>
<td>Positive impact on gut hormones</td>
<td>Vitamin AND Protein deficiencies</td>
</tr>
<tr>
<td>Greatest impact on diabetes</td>
<td>Critical to comply with followup care</td>
</tr>
<tr>
<td>Reversible = metabolisatry procedure</td>
<td>Irreversible = restrictive procedure</td>
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</tbody>
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Candidates for Surgery

1. More than 100lbs (45.5kg) overweight / BMI equal to or above 40
2. BMI equal to or above 35 with comorbidities related to obesity
   - Sleep apnea
   - Non-alcoholic fatty liver disease (NASH)
   - Dercytosis
   - Heart Disease
   - Hypertension
   - Type II Diabetes
3. Prior weight loss efforts attempted with no achievement of a healthy weight

Financials: Show me the Money!

Self-pay
- Gastric Bypass @ $23,000
- Gastric Sleeve @ $14,500
- Duodenal Switch @ $20,000 to $30,000
- Not including pre-surgery requirements

Website for coverage questions: www.obesitycoverage.com
CMS Requirements – Medicare Pays!

Procedure must be performed at a bariatric “center of excellence”
BMI > 35
Co-morbidity = 1
Documentation of obesity – minimum of 5 years
Physician letter
Passing score on psychological evaluation
Treatable conditions that result obesity must be eliminated
• Pituitary/adrenal disorders
• Thyroid disorders

Global Bariatric Healthcare” – Medical Tourism

Attractive to self-pay patients
Estimated to cost less than 40 to 80%
Questionable quality
Long distance travel post procedure may increase risk of complications
Infectious disease concerns

Gut Microbiome Effects of Bariatric Surgery

Decreased availability of nutrients
Decreased lipogenic signaling – systemically and throughout
Reduction of inflammation
Ratio of Firmicutes/Bacteriodetes decreased and reducing caloric extraction from carbohydrates in the gut
Change in bile-acid metabolism resulting in favorable metabolic processing of lipids and glucose
Possible Complications After Surgery

<table>
<thead>
<tr>
<th>COMPLICATIONS SEEN EARLY</th>
<th>LONG-TERM COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep venous thrombosis/pulmonary embolism</td>
<td>Erosion/slippage of the band</td>
</tr>
<tr>
<td>Dehydration/nausea/vomiting</td>
<td>Nutrient deficiencies</td>
</tr>
<tr>
<td>Leaking</td>
<td>Gallstones</td>
</tr>
<tr>
<td>Death</td>
<td>GI bleeding</td>
</tr>
<tr>
<td></td>
<td>Hernia</td>
</tr>
<tr>
<td></td>
<td>Dumping syndrome</td>
</tr>
</tbody>
</table>

Drug Absorption

- Dissolution of drug – solubility/pKa
- Diffusion of drug
- Surface area/transport/metabolism (OATP/PEPT1)
- Absorption at the drug’s primary site
- Circulation of blood to the GI tract for distribution – enterohepatic circulation
- Protein binding

Limited Data

- Very few randomized controlled studies focusing on medication use
- Available data is from obsolete procedures
- Very few consensus statements
- Available information is from small cohorts and case-reports
Dosage Form Considerations

Extended release or long acting: SWITCH to immediate release
Liquid dosage forms may be preferred – use sugar free to prevent dumping syndrome
Capsules – use those that can be opened and mixed in applesauce or water

Treatment of Pain – Post Surgery

Preferred medications
- Acetaminophen
- Tramadol
- Lidocaine patches
- Tramadol
- Opioids – use with caution due to constipation!

DO NOT USE NSAIDS!
Avoid NSAID containing topical formulations

pH Matters

Is the drug a weak acid or weak base?
What is the pKa of the drug (ionization)?
Examples:

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa Value</th>
<th>2010</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Apixaban</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>7.7</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Lixivatran</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Anticoagulation - warfarin

Daily doses of 10 to 20mg may be needed to be therapeutic.
INR's followed closely
Lower absorption – pka @ 5
Case reports are only source of information

Anticoagulation: Direct Oral Anticoagulants

Research is limited – research is increasing
Apixaban (Eliquis®) – favorable
- Unaffected by pH changes
- Lipophilic
- Concern – CYP and P-gp metabolism
Rivaroxaban (Xarelto®) – favorable
- Lipophilic
- Moderate CYP metabolism and no P-gp
- Exhibits the fastest time to peak concentration
Protecting the Heart

Examples:
- Aspirin
- Clopidogrel
- Prasugrel

Risk/benefit: Ulcers developing post-operatively – stop!
Cardiology consult – decisions made after reviewing each case individually

Prevention of Bone Loss

Parenteral products:
- Zoledronic acid administered 5mg IV annually
- Ibandronate 3mg IV quarterly

Nasal spray formulations:
- Calcitonin
- Teriparatide
- Raloxifene

All bariatric patients should maintain a regimen of:
- Calcium 600mg twice daily
- Vitamin D 400iu twice daily

Contraception – Oral Products

Absorption is varied
- Enterohepatic recycling could possibly render less effective
- Case Control Studies:
  - No significant difference observed with single doses of D-norgestrel, oestradiol, oestrone

Lower AUC of single doses of L-norgestrel or non-hormone resulted post-op

Alternatives to oral formulations:
- IUD
- Depo-Provera
- Nuvaring
Antibiotic Therapy

IM injections preferred when possible

Absorption and bioavailability challenges:

- Macrolides – absorption varied
- Sulfamethoxazole/trimethoprim – decreased bioavailability
- Nitrofurantoin – available to use but not the twice daily formulation (Macrobid®)
- Penicillin – case report showing 1g dose having an increased AUC (pKa 2.75)
- Ampicillin – reduction of bioavailability reported to be decreased by 109 – 141% post-op
- Levels of rifampin have been reported as reduced – data from 6 case reports

Thyroid Preparations

- Thyroxine
  - Titrated to TSH levels
  - Cases have been reported of patients requiring an increase in dose of 3 times their previous dose

- Propylthiouracil
  - No difference in bioavailability – one case report

Statin Therapy

- Simvastatin – prodrug that is lipophilic, unknown results
- Pravastatin – hydrophilic, exhibits moderate binding, metabolism is not substantial
- Atorvastatin – low bioavailability, CYP substrate, lipophilic, protein bound
  - Study results are varied
Beta-Blockers

Study from 2014 indicated patients requiring adjustment to doses for as long as 1 year after procedure

Propranolol
- Single dose trial indicated a 32% reduction of AUC and a Cmax of 20%
  - Basic and lipophilic – change in pH is a factor

Atenolol
- Basic and hydrophilic
  - Single dose studies did not show a difference

Pharmacotherapy for Depression

Absorption can be greatly affected
- Approximately 23% patients required a dose increase after procedure
- Remained at same dose – 40%
- Therapy change needed – 18%
- Discontinuation or change in therapy – 16%

Follow up necessary!

H₂ Antagonists and Proton Pump Inhibitors

Reduction in use of these drugs
- Sleeve gastrectomy patients – largest reduction in use exhibited
Supplementation to Maintain Nutrition

Macronutrient deficiencies – carbohydrates, fats, proteins

Micronutrient deficiencies (trace elements) – Vitamin A, D, E, K, and calcium
- Vitamin A – rough and dry skin (xerosis)
- Vitamin E – decreases antioxidant function and immune system
- Vitamin K – clotting factors
- Folic Acid – 1 to 2 mg daily **be careful – excess folic acid can hide a B12 deficiency
- B12 – intrinsic factor levels are decreased
  - 1000mcg IM every month or 5000mcg IM every 6 months

Pharmacist’s Role – Bariatric Team

- Pre-assessment of medications both prescribed and over the counter
- Assess for risk of thromboembolism
- Post-surgery discussions – help reinforce compliance

Pharmacist’s Role In the Community

- Keep lines of communication open – education
- Drug dosage form optimization
- Remember when recommending OTC medications to patients you are not familiar with, to ask those open ended questions, “Have you had any abdominal surgeries?”
- Make yourself aware of bariatric practices in your area and the services they provide
  - Support groups
  - Counseling
  - Dietician services
Defining Success

"Greater than or equal to 50% excess body weight loss at 5 years post-op." - NIH

Weight regain
- Increase intake of calories
- "Grazing"
- Decrease in activity
- Tolerance to increased intake
- Depression

Best Practices to Reinforce

Water intake must be a priority
Avoid carbonated beverages
Solid foods for meals or snacks – may use liquid protein supplements
Wait 30 minutes after eating to ingest liquids
Eat 4 to 5 small meals daily – meet with dietician for guidance
Avoid food with high sugar content
Protein intake – recommended 65 to 75 grams / day
Take your vitamins!

Questions/Comments