Obesity has become a worldwide health concern with a constantly rising prevalence. Obesity is defined by WHO as excess weight gain for a given height with BMI ≥ 30 kg/m^2. The prevalence of obesity in the US is 31%. Obesity is associated with increased cardio-metabolic risk, insulin resistance, type 2 diabetes due to increased cytokine production and sub-clinical inflammation. Besides diet and exercise, gut microbiome has been recognized as a major factor in the pathophysiology of obesity and dysbiosis can contribute to the pathophysiology of obesity.

Recent research results have suggested that the shift from healthy symbiosis to persistent dysbiosis can increase bacterial metabolites, such as short-chain fatty acids (SCFAs) causing host energy homeostatic changes, and elevate bacterial components, such as lipopolysaccharides (LPS) triggering low-grade inflammation leading to excess fat deposition and resultant obesity.

1. Dysbiosis causes increased diet energy extraction leading to obesity

Healthy human gut microbiota consists of over 1000 phylotypes classified into six bacterial phyla shown in Table 1: Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Actinobacteria and Verrucomicrobia. Gut microbiota comprises mainly (>90 %) Firmicutes and Bacteroidetes. The Firmicutes are Gram-positive bacteria including *Lactobacillus*, *Mycoplasma*, *Streptococcus* and *Clostridium*, while Bacteroidetes are Gram-negative bacteria and include about twenty genera and species, such as, *Bacteroides thetaiotaomicron*. Most of these organisms are usually benign inhabitants of the intestinal ecosystem coexisting with the host in a commensal and symbiotic relationship. But, a few can be pathogenic especially when they gain access to the circulation or peritoneal cavity.

Obesity-associated changes in gut microbiota

Phylum	Genera	Change trend
Firmicutes	*Bacillus*	↑
	Clostridium	↑
	Lactobacillus	↓
Bacteroidetes	*Bacteroides*	↓
	Prevotella	↑
Actinobacteria	*Bifidobacterium*	↓
Verrucomicrobia	*Akkermansia*	↓
Euryarchaeota (domain archaea)	*Methanobrevibacter*	↑

The composition of the gut microbiota is relatively diverse in healthy individuals. However, obese people are associated with a low bacterial gene count with a reduced proportion of Bacteroidetes and higher levels of Firmicutes. Increased Firmicutes is associated with energy intake than expended by the body causing weight gain and obesity. Research results have suggested that obesity due to energy imbalance is determined by the Firmicutes:Bacteroidetes (F:B) ratio. Obese gut microbiota exhibits significantly elevated F:B ratio while lean gut microbiota show preponderance of Bacteroidetes (up to 50 % more). Some obese individuals have shown up to 90 % less Bacteroidetes and much more Firmicutes than lean individuals. Consumption of high-fat/carbohydrate diet favors increased Firmicutes dominance.

Firmicutes play a significant role in the relationship between gut bacteria and human health and Firmicutes dominance can significantly increase energy harvest from diet. Firmicutes consists of diverse members. Many members including Lactobacillus, Faecalibacterium, Eubacterium, Roseburia, and Anaerostipes are capable of efficiently ferment dietary fiber and resistant starch to produce metabolites such as short-chain fatty acids (SCFAS), like butyrate, acetate, and lactate. Butyrate has many health benefits and helps prevent gut inflammation and fuels the gut lining cells. However, enhanced energy extraction from the diet can cause corresponding weight gain and obesity. In contrast, consumption of low fat and sugar diet increases Bacteroidetes dominance, which encourages weight loss by stimulating increased expression of fasting-induced adipocyte factor (FIAF) and subsequent increase in energy expenditure and reduced fat storage.

2. Dysbiosis promotes chronic inflammation causing liver inflammation, insulin resistance and obesity

Among the Firmicutes members, some of them are some pathogenic gram-positive species. For example, Staphylococcus aureus is a common cause of serious infection. Some other pathogenic members produce bacterial endotoxins which can cause chronic low-grade inflammation of the gut due to the initiation of sub-clinical, persistent

innate immune response. Such low-grade gut inflammation can disrupt the tight-junction of the intestinal epithelium cause increase permeability which allow enhanced passage of bacteria and bacterial LPS to the circulation. LPS is able to activate macrophages in different organs including adipose tissue and the liver resulting in the production of proinflammatory factors (factor nuclear Kappa B; NF-κB) and macrophage infiltration in adipose tissue. Adipocytes inflammation trigger systemic low-grade inflammation by releasing increased levels of proinflammatory mediators such as TNF-*α*, IL-1 and IL-6. These cytokines stimulate further release of cytokines and chemokines leading to lipogenesis and obesity by acting on adipocytes in a paracrine and/or autocrine fashion.

Insulin resistance plays a key role in the development of obesity. Insulin regulates blood glucose by stimulating glucose uptake and utilization by muscle and adipose tissues and inhibit hepatic glucose production. Increased cytokines such as TNF-*α* and IL-6 released by adipocytes are able to block the key step of insulin signal transduction with reduced glucose uptake causing insulin resistance especially in muscle. Inflamed adipocytes also secrete hormones such as Resistin which can reduce glucose uptake causing insulin resistance in adipose tissue.

Enlarged adipocytes output increase FFAs into circulation and result in more TAG stored in the liver causing fatty liver disease leading to insulin resistance. Excess triglycerides act as *a* toxin to liver cells and cause liver inflammation leading to increased glucose and VLDL output into the blood, since excessive triglycerides in the liver can activate specific enzymes that interfere with a key step of insulin signal transduction pathway and, therefore, impairs insulin action resulting in hepatic insulin resistance with increased hepatic glucose and VLDL output.

Increased blood sugar levels due to impaired insulin function stimulates the pancreas to secrete more insulin to control the blood sugar levels. Increased insulin levels enhance more free fatty acid delivery to the liver and further increase hepatic fat accumulation. Dysregulation of insulin function in adipose tissue can further increase its release of inflammatory signals. The combination of these processes creates a vicious cycle of metabolic dysfunction leading to obesity, hyperlipidemia and type II diabetes.

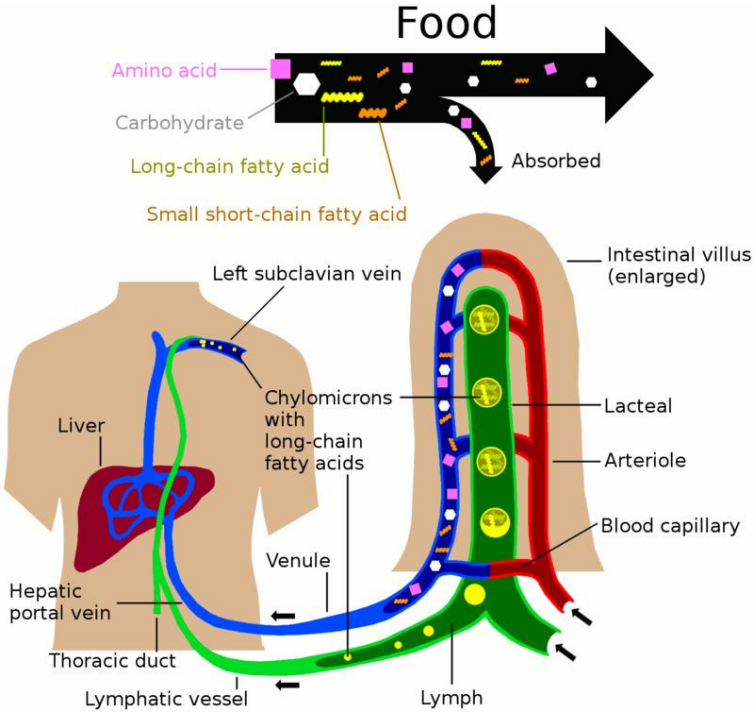
Increased insulin levels also suppress fasting-induced adipocyte factor (FIAF) expression in adipose tissue. Fat metabolism and storage is regulated by FIAF expressed in adipose tissue. Fat storage in peripheral white adipose tissue or lipogenesis is catalyzed by lipoprotein lipase. FIAF inhibits lipoprotein lipase activity and stimulates white adipose tissue lipolysis leading to a reduction in adipose tissue mass. Insulin suppresses FIAF activity and increased insulin levels due to insulin resistance block the lipolysis process causing obesity.

3. Dysbiosis causes GI Lymphatic Dysfunction and Obesity

A number of recent studies have shown that obesity is associated with lymphatic dysfunction and vice versa – lymphatic dysfunction promotes obesity. Lymphatic system functions as the 'sewage system' by removing body fluid and metabolic wastes from the cells and returning them to blood circulation. The lymphatic network consists of blind-ended capillaries located in most tissues that funnel into progressively fewer and larger pre-collecting and collecting vessels. Lymphatics in the gut perform essential transport and serve as a second line of defense against possible bacterial infections. In addition to collecting fluid, gut lymphatics also absorbs and transports dietary lipids through lymphatic capillaries, called lacteals, in the intestinal villi. Although most types of dietary nutrients are absorbed and entered to the portal vein for liver processing, dietary lipids or fat are absorbed in the GI lymphatic capillaries with the exception that small and medium chain fatty acid are passively diffused to the portal system. The collected lymph and lipid pass through the mesenteric adipose tissue and enter the mesenteric lymph nodes, ultimately entering into the venous circulatory system via the thoracic duct.

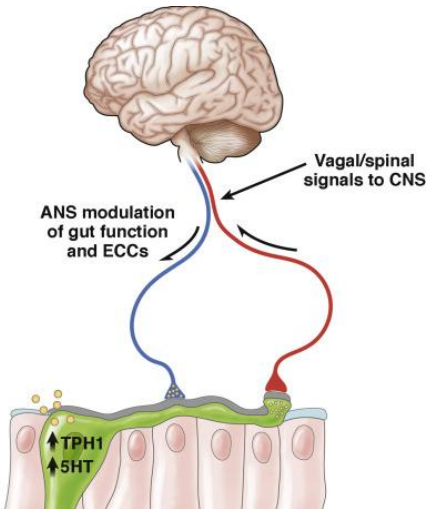
Damage to the intestinal epithelial cells due to bacterial infection and/or inflammation allow passage of bacteria pathogens and LPS into the villi interstitial space and subsequent drainage to the lymphatic system. The lacteals wall is not able to selectively avoid these toxins. Bacteria will be sequestrated in the mesenteric lymph nodes due to phagocytosis. The mesenteric lymph nodes function as a barrier to systemic spread for both commensal and pathogenic bacteria in the gut. The LPS in the gut lymphatic system then enter into the circulation with chylomicrons (fat globules) and are disseminated to the rest of the body causing inflammation in the liver and adipose tissue leading to insulin insensitivity and obesity.

Research has found that obesity is also associated with profound and progressive dysfunction of the mesenteric lymphatic system in mice and humans. The mesenteric lymphatic vessels and lymph nodes are completely surrounded by and embedded in visceral adipose tissue, resulting in a reciprocal interaction between the two.



Bacteria sequestrated in the mesenteric lymph node should be taken cared by the immune system in healthy individuals. However, when mesenteric lymph nodes have a chronic influx of bacteria, the immune system can become less effective and the lymph node can be blocked leading to difficulty to pass through the lymph node. In mice and humans with obesity, the mesenteric lymphatic vessels become highly branched and the diameter has been reduced with impaired pumping capacity and decreased transportation. Reduced lymphatic circulation with stagnating lymph within the lymphatic vessel leading to lymph leakage into visceral adipose tissue and the formation of highly branched mesenteric lymphatic vessels cause adipose tissue inflammation with further lipid accumulation and promote insulin resistance.

4. Enteric Nerves, Food Cravings and Obesity



The ENS senses and reacts to the dynamic ecosystem of the GI tract. The ENS communicates to the brain via brain-gut-axis which includes the vagus nerve and autonomic nervous system (ANS). Signals flow in both directions. The brain-gut axis is involved in many regular functions and systems within our body, including the regulation of eating. When food arrives in the stomach, certain peptide hormones such as cholecystokinin, glucagon-like peptide-1, and peptide YY are secreted. These peptide hormones bind directly and activate receptor targets in the brain and activate signaling pathways from the gut to the brainstem and the hypothalamus to stop food consumption. When we need to take in food before a meal on an empty stomach, the peptide hormone, Ghrelin is released from cells in the gastric mucosa to stimulate the brain to notify the person that they're hungry and increase food intake. Many undesirable gut bacteria can manufacture the peptide hormone Ghrelin. Overpopulation of undesirable gut bacteria will produce excessive amount of Ghrelin leads to increased hunger, as well as cravings for food, sugars, sweeteners and carbohydrates which leads to bloating, poor digestion, and weight gain.

Enteric nerve function can also be affected by chronic gut inflammation and poor mesenteric lymphatic circulation leading to altered neural signal of the enteric nerves creating sensation of food craving especially cravings for carbohydrates or fats.

Wellness Recommendation

To help patients achieve a healthy weight, Reduce 4 is recommended to address the root cause of obesity. Ingredients in Reduce 4 help reduce weight through the following mechanisms.

1. Reduce gram-positive bacterial population and clear pathogenic bacteria to resolve gut dysbiosis

Berberine is a major herbal ingredient in Reduce 4. Berberine is a plant alkaloid with many therapeutic effects. Its

anti-obesity action has also been well-documented. Berberine exhibits potent antibacterial activity against gram-positive bacteria and, therefore, helps reduce the population of gram-positive bacteria in the gut including pathogenic bacteria such as Streptococcus agalatiae. Berberine also enhances the expression of the AMPK-dependent adipose tissue triglyceride lipase leading to long-term weight loss and prevention of obesity. It helps regulate blood sugar level, LDL levels and decreases insulin resistance. It also has an anti-inflammatory property which help reduce gut inflammation.

Herbal ingredient Rhubarb, also in Reduce 4, has been suggested as a long-term weight loss or management therapeutic. Rhubarb extracts and compounds have also shown strong broad-spectrum antibacterial activity against pathogenic Gram-negative bacteria, *E. coli* and *Aggregatibacter actinomycetemcomitans*, and Gram-positive bacteria, *S. aureus*. It preferentially kills slow-growing bacteria and has shown great potential as a strong bactericidal antibiotic and as an anti-proliferative drug.

Rhubarb also has shown preventative effects against high-fat/high-sucrose diet induced obesity, diabetes, visceral adiposity, adipose tissue inflammation and liver triglyceride accumulation, without any modification in food intake in animal model. Such prevention effect is associated with a blooming of *Akkermansia muciniphila,* which is strongly correlated with increased colon expression of *Reg3γ*, an antimicrobial peptide that maintains the distance between the gut bacteria and the host which prevents bacterial translocation and regulates intestinal inflammation. Rhubarb supplementation also helps maintain gut barrier integrity by increasing goblet cell number and mucus production.

Components such as hydroxyanthraquinones (HAQs), from rhubarb have been shown to exhibit antiadipogenic activity to lower the body's lipids and has been recommended as a potential therapeutic for obesity management. Rhubarb HAQs efficiently suppress lipid formation in differentiated adipocytes and promote fat loss in vivo. Rhubarb HAQs also exhibit superior inhibition of BUN, CRE, AST, ALT, and total cholesterol levels. The steatosis hypertrophy was significantly diminished by the treatment of rhubarb HAQs.

If patients have a diagnosed strep and/or staph infection of the gut, Trinicin is also recommended. Trinicin helps clear gut pathogenic gram-positive bacterial infections and reduce gut inflammation. Probiosis may also be required to clear other types of pathogenic bacteria from the gut. Patients with severe constipation, PA may also be required to clear the infection and inflammation from the pancreas, duodenum, and small intestines.

2. Reducing Liver Inflammation and insulin resistance

Herbal ingredients in Reduce 4 have also been shown to increase energy metabolism, lower total cholesterol, increase lipid export, and reduce fatty liver deposits. They help improve blood circulation through the hepatic artery to provide adequate oxygenated blood flow to the liver to improve the function and structure of the liver to help aid the breakdown of fats and increase insulin sensitivity to promote weight loss.

Red Peony Root has been shown to have powerful healing properties within the human body. It decreases proinflammatory cytokines and is commonly used in the treatment of chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and hepatitis. This herb can help reduce the low-grade inflammation and the resulting metabolic syndrome in obese patients. Research has also shown that the compound paeniflorin in Red Peony Root can help increase probiotic activity in the gut, which can help balance gut bacteria in the body and prevent intestinal inflammation.

Cassia obtusifolia seed have been used as an effective medicinal food for the prevention and improvement of fatty liver disease. Clinical research has shown that oral administration of processed Cassia obtusifolia seed powder reduces body weight and cholesterol in overweight patients. Compounds in Cassia obtusifolia seed can inhibit αglucosidase and human protein tyrosine phosphatases 1B to restore insulin sensitivity.

Herbal ingredient King Solomonseal Rhizome has been shown to lower serum total cholesterol, triglyceride and fasting blood glucose, improve glucose tolerance test and insulin tolerance test.

3. Improve lymphatic circulation

Herbal ingredients in Reduce 4 have also been shown to help improve GI and systemic lymph fluid recycling and circulation to reduce lymph leakage and promote weight loss. In Traditional Chinese Medicine (TCM) terms, the herbs exert their effects by clearing phlegm damp and removing Qi stagnation.

Animal studies showed that Perilla Seed Oil alleviates gut dysbiosis, intestinal inflammation and metabolic disturbance in obese-induced-insulin-resistant rats. Treatment with Perilla Seed Oil not only effectively attenuated HFD induced gut dysbiosis, but also improved gut barrier integrity and decreased gut inflammation. It helps decrease oxidative stress, metabolic endotoxemia, and insulin resistance. Improved gut integrity will in turn help the GI lymphatic system to avoid toxin damage and restore its normal functionality.

White mustard seeds have been traditionally used as a weight loss ingredient which also has various health benefits. It helps stimulate the lymphatic system for improved lymphatic drainage which helps reduce lymph edema and swelling to aid in weight loss. Mustard seeds contain compounds that help increase metabolism and help the body burn more calories to support weight loss. Mustard seeds are rich in compounds that can help reduce appetite and cravings to help reduce overall calorie intake. It also helps regulate blood sugar levels, preventing spikes and crashes in energy levels and improve digestion and promote healthy bowel movements. Mustard seeds contain anti-inflammatory compounds, which can help reduce inflammation to aid in weight loss.

Qiancao, also known as Rubia Cordifolia Root, has powerful beneficial effects on the lymph system and has been known as a powerful lymph cleanser. This bitter, astringent herb was traditionally used and valued for its extreme effectiveness in cleansing and purifying the blood, liver, and lymphatic system. It supports the lymphatic function by allowing nutrition to feed the cells and wastes to be removed from the body in an optimal fashion. It is known to

4. Restore healthy appetite regulation

Herbal ingredients in Reduce 4 such as Berberine and rhubarb help reduce undesirable gut bacteria and inflammation. This may help alleviate the negative influence on the expression and signaling of GI peptide hormones to restore healthy appetite regulation and reduce food cravings. Herbal ingredient in Reduce 4 also have been shown to function as appetite suppressants to help reduce food intake to support weight loss.

Ginseng has been shown to have anti-obesity effects in high-fat diet-fed rats. Research on rats demonstrated that several ginsenosides reduce HFD-induced obesity and adipose tissue mass by controlling appetite and food consumption as well as attenuating HFD-induced chronic inflammation of the hypothalamus, improving leptin resistance, and regulating the hypothalamic secretion of neuropeptide Y and CCK.

Ginseng also demonstrated other health benefits which can be more beneficial to obese patients including reducing inflammation, lowering blood sugar and cholesterol levels, as well as reducing oxidative stress and increasing energy production in cells to help decrease fatigue. Ginseng possesses potent anti-bacterial, anti-fungal, and anti-viral properties and may enhance the function of the immune system.

Astragalus has also been shown to possess an anti-obesity effect in HFD fed mice by suppressing appetite and increasing leptin sensitivity by enhancing leptin signaling transduction. More specifically the components, Astragaloside IV in astragalus can prevent obesity and weight gain by enhancing expression of leptin and its receptors, as well as leptin sensitivity. Astragaloside IV also helps reduce blood sugar levels, lower serum triglyceride and total cholesterol levels, mitigate liver lipid accumulation, reduce fat tissues and decrease the enlargement of adipose cells. Astragalus also is used to protect and support the immune system through protecting the liver.

Expected Results and Timeframe

Patients can experience less bloating, better digestion, increased emotional stability and stress tolerance, enhanced energy levels, and a change in eating habits with less cravings for sugar, sweeteners and carbohydrates in 2-3 weeks and reduced body weight in 4-6 weeks. 3 months of the protocol is recommended for significant improvement in the body weight. It is recommended to continue taking Reduce 4 to help prevent weight gain.

Patients who have strep, staph and other pathogenic gut infections can experience weight reduction in 1-2 weeks with the additional treatment of Trinicin, Probiosis and/or PA. 3 months of the protocol is required to clear staph infections in the gut and 6 months of the protocol is required for strep infections in the gut.

Selected Case Study

Removal of Gastrointestinal Strep Infection with Trinicin
Erin Thole, CNHP, TX

A 57-year-old woman presented with chronic inflammation, severe joint pain and swelling, uncontrollable weight gain despite eating a low-calorie diet and a very active lifestyle. Her stool panel shows strep infection along with multiple other bacterial infections in the gut. The stool panel also shows her IgA immune system in overdrive as a result of these chronic infections.

She was put on a gluten free, high protein diet. She was given Zinzino Balance Oil to help control chronic inflammation and joint swelling which allowed her to go off her prescription anti-inflammatory medication. The Balance Oil also helped to get her blood pressure in range, and she discontinued her blood pressure medication with no issues, maintaining a healthy blood pressure around 112/78.

I recommended that she start taking Trinicin from Wei Labs to get rid of the high levels of strep in her gut as well as Probiosis to get the other bacterial infections under control. She started losing weight immediately. Her energy was great, her brain fog went away, her digestion improved immensely, and her chronic inflammation subsided.

She lost 32 pounds within 7 months and feels years younger. Her gut ecosystem has improved greatly within this time as well. All infections are gone.

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