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Short Communication

Redefining the Clinical Approach to the Treatment of Obesity

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- Clinical practice
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- Healthy diet

Abstract

Background: Regardless of how physicians and patients have treated obesity, prevalence continues to steadily increase to the point of being an epidemic within the United States and now global pandemic. Therefore, there is immediate need for a shift in how patients and health care providers understand the condition in terms of gut microbiome functionality as well as the impact diet has on the health of the gut microbiota.

Significance: Here we illustrated the need for patients to redefine their ideal of a healthy diet as many now consume processed foods including low-fat and or fat-free foods in place of fresh-whole foods. A factor significantly contributing to weight gain as processed foods are low in natural plant fiber and designed in induce repetitive eating behaviors.

Aim: We aimed to provide physicians, nutrition and mental health specialists with relevant information regarding the clinical management of obesity which includes the redefining of the disorder as a human condition in terms of the gut microbiota. Additionally, we presented a new perspective in approach to treatment with focus on diet and eating habits as these factors are directly correlated with negative affects on the gut microbiome.

Conclusion: Ultimately, collaborations among the patient and their health care providers are now of even greater importance as the future of overweight and obesity management lies within the relationship between the human host, their diet and the residential gut microbiota.

ABBREVIATIONS

NIH: National Institutes of Health; FDA: Food And Drug; CDC: Centers For Disease Control and Perve Regardless of the Approach to Treatment Established between the Physician and Patient; Obesity Prevalence Continues to Steadily Increase to the point of now being an Epidemic within the United States and Global Pandemic. Tion; Administration; SCFAS: Short-Chain Fatty Acids; TID: Three Times Daily; OTC: Over the Counter Medication; BID: Twice Daily; QD: Once Daily; LPS: Lip Polysaccharide

KEY TERMS

Gut Microbiota- the specific species of bacteria residing with the distal large intestines which constitute the numerous populations of the gut microbiome; Gut Microbiome- the specific bacteria, their collective byproducts and expressed genes function as an energy extractor of undigested plant fibers and polysaccharides; Early Phase Gut Microbiome Dysbiosis (EP-Gut Dysb)- a condition occurring in normal weight persons within the gut microbiome whereby fundamental shifts of the Firmicutes-Bacteroidetes phyla ratio resulting in gut microbiota functionality disruption; Late Phase Gut Microbiome Dysbiosis (LP-Gut Dysb)- following (EP-Gut Dysb), the physical manifestation of symptoms and deterioration of overall health within the individual resulting from long-term disruption in gut microbiome functionality; Chronic Gut Microbiome Endotoxemia (Chronic-GME)- a biological cycle occurring within the gut microbiome of individuals in (LP-Gut Dysb) whereby the increased amount of lipopolysaccharide (LPS) produced by the gram negative bacteria of the Bacteroidetes phylum cause a systemic inflammatory reaction within the human host; Gut Microbiome Adiposity (GM-Adip)- a progressive, physical condition occurring as a result of (LP-Gut Dysb) and Chronic-GME) whereby the individual presents with systemic increases in body fat[formally known as obesity].

INTRODUCTION

The first official medical recording of obesity is attributed to Hippocrates who reported findings during (460 B.C - 370 B.C). According to his writings causation was due to an over indulgence of food which manifest in vivo as increased body fat; a fundamental ideal still applicable in modern day [1]. However, for centuries of human history obesity was perceived as a sign of wealth and good health. The social acceptance evolving as human populations who once faced food scarcity and malnutrition, were for the first time experiencing an abundant access to food [2]. Advancements in food manufacturing spawning shortly after the Industrial and American Revolutions have continued to expose humans to a vast array of energy dense, nutrient poor food products designed to induce food cravings and drive eating behaviors [3]. Now, many global human populations live in nations where conditions such as obesity present higher morbidity risk than malnutrition [4]. An understandable occurrence as food manufactures employ marketing strategies such as 'floating supermarkets' targeted towards 'low-income consumers' residing along the Amazon River and in other remote villages [5]. With more manufactures following suit, even the most primitive of humans face an increased risk of developing overweight and obesity.

As the second leading cause of preventable death in Unites States, obesity poses serious threats to national and state-level health budgets with healthcare costs currently ranging from $147 to $210 billion annually [6,7]. These costs are in spite of >$25 billion annual consumer spending on numerous over the counter (OTC) dietary supplements and weight loss products, along with the 2.7 million patients who have been prescribed an obesity treatment [8]. Regardless of the approach to treatment established between the physician and patient, obesity prevalence continues to steadily increase to the point of now being an epidemic within the United States and global pandemic. Twenty-two states have ≥35% of the adult population diagnosed as obese and no state has <20% obesity among the adult populations [9]. Considering that diet type as a well known factor contributing to overweight and obesity, in a twelve year study including (n=157,142 households) researchers reported >80% of the food calories within the home were from prepared meals or foods that were high in sugar, fat and salt. Findings suggesting this diet type known as 'Westernized diet type' are highly prevalent within the United States [10]. With these understandings, the questions arise regarding why obesity prevalence not only remains despite costly national, state and individual level interventions, but also continues to exponentially increase. Through the following commentary we aim to provide physicians and nutrition specialists with new and relevant information regarding the clinical management of obesity. This includes the redefining of the disorder as a human condition representative of a symptom of evolutionary discord between humans and their gut microbiota. Additionally, we present a new perspective in approach to treatment with focus on diet and eating habits as these factors are directly correlated with negative affects on the functionality of the gut microbiota.

Currently approved obesity treatments

In 1985 National Institutes of Health (NIH) recognized obesity a major threat to public health requiring immediate state-level interventions to assess the impact. With prevailing overweight and obesity rates across the United States, the earliest treatment therapies launched in the late 1940s through late 90s, were amphetamine based pharmacological appetite suppressants. However, the resulting amphetamine abuse resulted in an epidemic addiction within the U.S. causing the removal of the products from clinical practice [11]. Today, the medical treatment of obesity is still fundamentally based upon a patient centered approach aimed at reducing the amount of systemic adipose tissue, the primary symptom of overweight and obesity. Current management plans also include increasing physical activity, food portion control, eating behavior modification therapy, the monitoring of body mass index as well as dietary fat and or calories [12-15]. Additionally, NIH also recommends the prescribing of pharmacological agents and in extreme cases surgical intervention for the appropriate patients. Therapies approved by the Food and Drug Administration (FDA) indicated for short and long-term treatment of obesity is summarized in (Table 1). Investigating product package inserts, it is evident patients must be willing to commit to life long pharmacological treatments with some therapies requiring multiple daily dosing. Additionally, in extreme cases obese patients must endure an invasive surgery that in many times may only be a temporary solution [16-22].

As more patients seek prescribed treatments as part of obesity management, many major health insurance providers are dropping prescription coverage from their plans leaving the individual to cover costs and or without needed medical intervention. Challenges in pharmacologically based therapies also include the perceptions of a high risk-benefit ratio coupled with limited product efficacy held by both physicians and patients. Researchers polling physicians (n=130), found that only one-third of the physicians felt they were well equipped to treat obesity. This was primarily due to the lack of training and support needed for obesity treatment coupled with lack of efficacious therapy options. Overall, many physicians did not report prescribing pharmacological treatments for obesity, but rather an increase in rigorous exercise along with the consumption of a low calorie-fat diet. These findings suggest it would be of significant benefit to patients' health as well as to the overall success of obesity treatment, for researchers to develop safer, more cost and therapeutically effective therapies targeted to the root cause of obesity rather than merely treating the symptoms [23-26].

Redefining obesity

Albeit, the questions still remain to why obesity prevalence continues to rise as well as why currently prescribed treatment therapies are associated with high rate weight gain relapse [27,28]. The answer to these questions lies within the understanding that diet is directly linked to the health of the human gut microbiota (specific species of bacteria constituting populations of distal large intestine), and that diets such as a Westernized regime affect the gut microbiota in ways that cause diseases and disorders including obesity, heart conditions, autism, type 2 diabetes, cancers, mood-behavior disorders, intestinal disorders and many others [29,30]. While increasing physical activity is a well known factor significantly contributing to obesity

Table 1: Summary of Pharmacological and Surgical Agents FDA Approved for the Treatment of Obesity: Provides a summary of Food and Drug Administration currently approved therapies used for the short and long-term treatment of obesity. As shown, it is evident pharmacological treatments require lifelong commitment and many are multiple daily dosing, injections and or invasive surgery. As prescription coverage is dropped, the costs are left up to the individual; leaving most to turn to extreme dieting measures appetite suppressants and or fat burners that target only the symptom of weight gain.

Pharmaceutical-Surgical Agent	Dosage-Administration	Indication
1999* Xenical (orlistat)® fats	120 mg capsule t.i.d.♦	Inhibits absorption of dietary
2007 Alli (low dose orlistat) ®	Available OTC*	Same as Xenical (orlistat)®
2012 Belviq (lorcaserin) ®	10 mg tab b.i.d. (Lifelong)	Appetite suppressant simulating neural activity controlling hunger
2012 Qsymia (phentermine) (phentermine-topiramate) ®	3.75-15 mg tab q.d. (Lifelong: titrate up)	Appetite suppressant & treat epilepsy-migraine
2014 Contrave dependence (naltrexone-bupropion) ®	8 mg-32 mg tab b.i.d.(Lifelong: titrate up)	Treat opioid-alcohol (naltrexone) & treat depression (bupropion)
2014 Saxenda (liraglutide) ® improves	0.6 mg-3 mg injection q.d.(Lifelong: titrate up)	Weight loss properties; glycemic control in type 2 diabetes
2015 ReShape Dual Balloon ®	Oral Endoscopic Procedure (Temporary implant <6month)	Reduces Food Intake: specific mechanisms unknown
2015 Maestro Rechargeable System ® mechanisms	Surgical Implant	Weight Loss: specific unknown.
2015 Lap-Band System ®	Surgical Implant	Reduces food intake & increases digestion time

prevention and treatment, the factor of diet plays an even greater role as it also serves as food for the residential gut microbiota. Now, as researchers understand the impact of diet on microbiota functionality, there is an immediate need for redefining and revitalizing the approach to obesity. Theoretically, obesity is a human condition indicative of a symptom of evolutionary discord between humans and their gut microbiota occurring as the once all natural and primarily plant based diet once consumed by ancestors is replaced with a disproportionately greater amount of processed foods and decreased natural plant fiber.

As depicted in (Figure 1), in a healthy state the primary role of the gut microbiota and the collective gut microbiome (the specific bacteria, their byproducts and expressed genes), is to function as an energy extractor of undigested dietary plant fibers and polysaccharides [31]. Using the natural plant fibers, the gut microbiota ferment them into short-chain fatty acids (SCFAs); propionate, butyrate and acetate [32,33]. SCFAs are vital nutrient molecules utilized by both the gut microbiota as well as human cells throughout the body and are they are also involved in many metabolic processes affecting energy homeostasis, appetite regulation and food intake. All SCFAs have anti-inflammatory properties and can prevent infiltration of immune cells from the bloodstream and into adipose tissue. Butyrate is reported to have more profound anti-inflammatory effects than acetate and propionate. Of the three, acetate is systemically present in higher concentrations than butyrate and propionate. However, researchers theorize acetate and propionate are most likely to directly influence changes in adipose tissue as they are potent activators of FFA2 cell receptors that are found on the cell membranes of adipocytes. While murine studies have demonstrated the propensity of SCFAs to inhibit weight gain, there is a paucity of such evidence to support these findings within humans [34,35].

Species level or 'structural' changes in the types of bacteria constituting the populations of the gut microbiota, results in a condition referred to as gut microbiome dysbiosis which is associated with the causation of many diseases including overweight and obesity. Fundamentally there is a shift in the Firmicutes-Bacteroidetes phyla ratio with Bacteroidetes prevailing [36]. The most significant factor contributing to gut microbiome dysbiosis besides the use of antibiotics is the type of diet consumed by the human host starting at

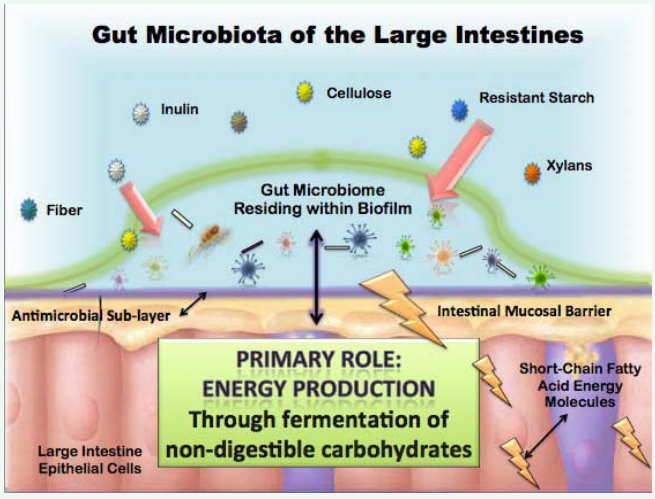

Figure 1 Depiction of Human Gut Microbiota within Natural Habitat of Distal Large Intestine: The human gut microbiota constitute (10^{12-14}) of microorganisms per (ml) of colonic material equating to ≈1.3 kilogram mass of primarily bacteria cells or 95.0% of the total cell number within the human body. The gut Microbiome also collectively contributes ≈20 million genes to the total human genomic profile. The microbial biofilm (shown in green) is maintained as a separate entity by an antimicrobial layer (shown in purple) generated by the intestinal epithelial cells. In a healthy state, the gut Microbiome function primarily as an energy extractor of undigested plant fibers and polysaccharides, producing short-chain fatty acids including acetate, butyrate and propionate.
*Year of FDA approval. ♦t.i.d: three times daily; OTC: over the counter medication; b.i.d: twice daily; q.d.: once daily.

birth. As summarized in (Figure 2), gut microbiome dysbiosis clinically presents with an early and late phase. Early phase gut microbiome dysbiosis (EP-Gut Dysb) is a condition occurring in normal weight persons within the gut microbiome whereby fundamental shifts of the Firmicutes-Bacteroidetes phyla ratio results in gut microbiota functionality disruption. EP-Gut Dysb is physically asymptomatic and only detectable through diagnostic microbial DNA screening of patients' stool along with analysis of detailed medical and dietary history. This phase serves as the best time for dietary interventions. Late phase gut microbiome dysbiosis (LP-Gut Dysb) follows (EP-Gut Dysb) as the physical manifestation of the long-term disruption in gut microbiome functionality. Clinically presents as overweight and or with deterioration in overall health of the individual. Patients in (LP-Gut Dysb) may benefit from probiotic and or microbial fecal transplant therapies. Chronic gut microbiome endotoxemia (Chronic-GME) refers to the biological cycle occurring within the gut microbiome of individuals in a state of (LP-Gut Dysb) whereby the increased amount of lipopolysaccharide (LPS) produced by the gram negative bacteria of the Bacteroidetes phylum, cause a systemic inflammatory reaction within the individual. Since (LPS) is toxic to humans, the over abundant amount causes different intensities of inflammatory cascades which range from an overweight to obese reactions [37-40]. Fundamentally, the inflammation associated with obesity is very distinct from that of classical inflammation as overweight and obese inflammation are associated with a low-grade, systemic inflammation involving the induction of inflammatory cytokines such as TNF-α, IL-1β, and CCL2, increases in mast cells, T cells and macrophages as well as increased inflammation within adipose and liver tissues [41-43]. Gut microbiome adiposity (GM-Adip) defines the progressive, physical condition occurring as a result of (LP-Gut Dysb) and (Chronic-GME) whereby the individual presents with abundant systemic body fat. Obesity is defined as or in new terms, adiposity [44].

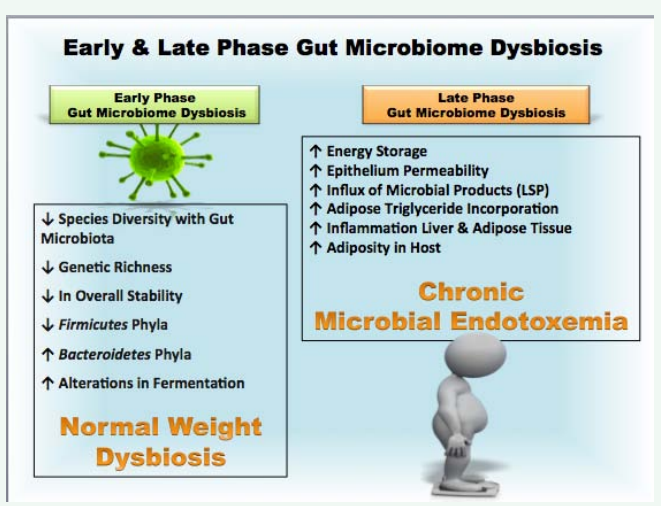

Figure 2 Microbial Endotoxemia Role in Pathogenesis of Adiposity: Early phase dysbiosis (EP- Gut Dysb) is primarily physically asymptomatic (e.g., normal weight dysbiosis) and only detectable through diagnostic DNA sequencing screening of patient stool sample and analysis of medical and dietary history. There is consensus among researchers that consumption of a high fat diet or one low in natural plant fiber directly influences the ability of the gut microbiota to harvest and store dietary energy. Such diet types induce increases in the production of short-chain fatty acids within the microbial community, which in turn induces systemic inflammatory response within the host. Occurrences of late phase dysbiosis (LP-Gut Dysb) are most familiar to physicians as it presents with systemic weight gain.

Redefining clinical approach to obesity treatment

Going forward, it is apparent the treatment of many diseases and disorders will require serious consideration of the gut microbiota as well as their role in human health [45]. In terms of overweight and obesity specifically, the close collaborations among the patient, their physician, nutritional and mental health professionals are now of even greater importance as the future of managing these disorders lies greatly within the health residential gut microbiota [46] Ultimately, shifting the perception of causation from being the result of overeating and lack of exercise, to being a symptom of dysfunction within the gut microbiome is also necessary to successful clinical management [47].

Diet is the most direct route for therapeutic intervention of overweight and obesity and has potential to directly increase the health of the gut microbiome more so than other treatment modalities [48,49]. According to 2010 nutritional guidelines set forth by the Centers for Disease Control and Prevention (CDC), recommendations for a healthy diet include a caloric intake that does not exceed the energy burned during daily physical activity and to increase the consumption of whole grains, vegetables and fruits. Additionally, CDC reports to consume low-fat or fat-free dairy products and seafood as well as to decrease the intake of sodium, saturated fats, sugars and refined grains [50]. Considering the health of the gut microbiota, there is overwhelming evidence supporting a natural, high fiber diet as being beneficial. Such diet is associated with enhancing the species diversity among the gut microbiota populations and it provides the nutrient SCFAs used by them as a food source. The required specific concentrations of SCFAs are reported to include acetate (40 mM) and both propionate and butyrate (20 mM) [51].

However, fundamentally food-processing procedures interfere with nutritional components of foods through alterations of micronutrient density, glycemic load, fatty acid composition, macronutrient composition and the sodium-potassium ratio [52]. The processing of plants in particular including methodologies such as grinding, grating, leaching, soaking, fermentation and heat treatments break down the plant cellulose making it easier for humans to digest, but removing the fiber needed by gut microbiota [53]. The health risk to the gut microbiota and human host is recognized molecularly as SCFAs also have the propensity to induce a systemic inflammatory reaction occurring as the energy dense Westernized diet exponentially increases the intestinal availability of SCFAs and alter metabolic pathways of the gut microbiota [54].

While a high fiber diet is quintessential in the prevention and treatment of overweight and obesity, management is also intricately tied to helping patients understand factors that drive their eating behaviors and influence their daily dietary choices. It is well documented that highly processed foods containing refined

grains, fats and sugar are purposely designed to induce repetitive eating and food cravings. The addiction potential related to consuming these foods is equated to ingesting heroin as the same pleasure center activation and neurotransmitter release occurs within the brain when stimulated by either source of stimulus [55]. Additionally, food manufactures also package processed food in ways that increase the likelihood of food addictions as well as that customer will consume more of the product in one serving. Tactics implemented by increased portion availability, disproportionately lowering cost providing more food for less than the cost of natural-whole foods and by creating eatery atmospheres that significantly contributes to repetitive eating behaviors [56]. As depicted in (Figure 3), there are several key measures that physicians and other health care professionals can immediately incorporate into clinical management overweight and obesity.

CONCLUSION

In conclusion, we illustrated the need for a fundamental shift in how patients, physicians and health care providers approach overweight and obesity management within clinical practice. An ideal now realized as the disorders manifest more so as result of dysbiosis within the gut microbiota than as poor dietary and lifestyle choices of an overweight or obese individual. We also illustrated the need for physicians and patients to redefine the ideal of a healthy diet as many patients now consume processed low-fat and or fat-free foods in place of fresh-whole foods. A factor significantly contributing to weight gain, as processed foods are low in natural plant fiber and designed to induce repetitive eating behaviors. Ultimately, the future of overweight and obesity prevention and treatment lies within the relationship between the gut microbiota and human host [57].

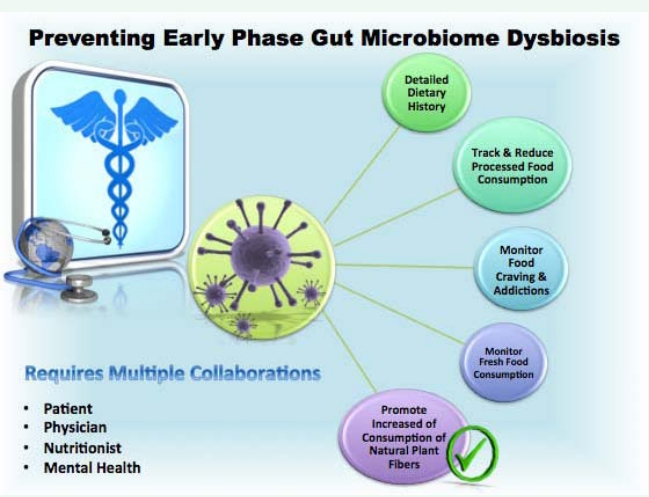

Figure 3 Clinically Based Methodologies for Preventing Gut Microbiome Dysbiosis: Shown are key measures that physicians and nutrition experts can easily implement into overweight and obesity management. The most significant factors being increasing natural plant fiber intake and decreasing intake of processed foods. Understanding overweight and obesity are intricately woven biological and environmentally disorders, it is also beneficial for patients to redefine their ideal of a healthy diet.

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