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The Role of the Intestinal Microbiota in Obesity by Warren Burke

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Abstract

The gut microbiota collectively act as a metabolic organ supplying energy for themselves and for the host they inhabit. This symbiotic relationship begins at the onset of a human birth and continues throughout the lifespan. Who identifies as the more robust symbiote has yet to be identified. The number of bacterial cells to human cells reveals a staggering disparity. The majority of estimates place the total number of microbial cells on and in the human body at 100 trillion, while the whole of the human contains 10 trillion. The bacterial versus human genome is equally disconcerting as the number of bacterial genes just within the human gut is estimated to be 3.3 million, while the whole human genome contains approximately 20,000. Who controls whom? We live in a mutual coexistence with our gut microbiota, but this affiliation occasionally becomes pathological, such as in obesity. The evidence points towards the increased energy harvesting capabilities by the intestinal bacteria promoting greater caloric availability to the host, thus allowing for prodigious adiposity stores. The medical provider can accomplish effective mediation through education. Not surprisingly, this education includes: increasing the number of vaginal deliveries, reinforcing the need for breast feeding, decreasing unnecessary antibiotic administrations, adopting a long-term low fat, high fiber diet, and committing to long-term regular exercise. Key words and headings used for this literature review included: microbiome, bacteria and obesity, gut bacteria, perturbation of microbiota, antibiotics and obesity, commensal bacteria, sub-therapeutic antibiotic therapy, brain-gut-axis or BGA, microbiota-gut-brain axis or MGB axis, and human microbiome project.

The Role of the Gut Microbiota in Obesity

The number of obese adolescents and adults in the United States has risen to an all-time high of 53.5 percent of the population, and continues on a steep vertical trajectory (CDC, 2015). The Centers for Disease Control estimates 80 percent of the population within the United States will be considered obese by the year 2030, and 100 percent by the year 2048 (CDC, 2015). This epidemic is not isolated to the United States, as worldwide obesity rates have more than doubled in the last twenty years (Devaraj, Hemarajata, & Versalovic, 2013). The obesity epidemic affects all races, ages, genders, and socioeconomic strati. As obesity rates increase, so do obesity related diseases, such as hypertension, diabetes, cancer, and heart disease. Not only does obesity escalate morbidity and mortality rates, but also conveys individual, communal, and pecuniary consequences (Buhman, Roux, & Bueter, 2014). The prevailing wisdom, on the genesis of obesity, has been predicated on the notion that an increase in caloric intake coupled with a decrease in physical activity results in weight gain for anyone, regardless. While this element is true, it is not an absolute verity (Devaraj, Hemarajata, & Versalovic, 2013). There are numerous factors and dimensions, which play a role in how an individual attains the status of obese. One such factor that has eluded scrutiny involves the ubiquitous microscopic life forms known as bacteria.

Bacteria occupy almost every surface on Earth, but humans were oblivious to their existence until 1665 (Yong, 2016). Anton van Leeuwenhoek was not only the first human to directly observe microscopic life in the world around him, but also the first human to observe bacteria on his person, where in 1683, van Leeuwenhoek took samples from his teeth and observed bacteria (Yong, 2016). Two hundred years would pass before

bacteria would be identified as the progenitor of disease. The genesis for the germ theory began in 1865 when French chemist Louis Pasteur demonstrated that bacteria were responsible for decomposition and fermentation and later, it was theorized that bacteria were responsible for disease (Yong, 2016). Pasteur's experiments in germ theory were replicated and scientifically proven by German physician and Nobel Prize winner Robert Koch, in 1884. The late 19th century birthed a new secular worldview as Charles Darwin's concept of the relationship between living entities as a battle for existence emerged. As a result of this conflict between the macro and the micro biospheres, it was soon theorized that freedom from bacteria equated with independence from disease (Yong, 2016). It was not until the turn of the 20th century that microbiologists began describing bacteria as mutualistic and not solely in terms describing pathology of disease. The devastating world war and the ensuing epidemics in the initial decades of the 1900's lead to the innovation that would severely curtail the reign of microbes and have unforeseeable consequences.

Sir Alexander Fleming's accidental discovery of penicillin in 1928 spawned a pharmaceutical industry with over 100 antibiotics to date, and as a result, this discovery has saved countless lives the world over (Collen, 2015). The attempted eradication of opportunistic and pathogenic bacteria via antibiotics has improved morbidity and mortality for those facing infections, and many individuals do not have the fear of death or dismemberment that once afflicted people of two to three generations ago. In the aftermath of 88 years of attempted global bacteriocide comes the unintended consequence of an altered human microbiome, most notably within the individual's small and large intestines. The ensuing dysbiosis leads to life threatening *Clostridium difficile*

infections, numerous antibiotic resistant microbes, and may be a contributing factor in the obesity epidemic. The aim of this literature review will be to identify the microbiota within the human gut, recognize how microbial life interacts with the host, and finally ascertain how the human intestinal microbiota make a contribution to obesity.

Theoretical Framework

In an effort to direct this review of literature, the influences of the gut microbiome will be investigated utilizing Betty Neuman's Systems Model nursing theoretical framework. Neuman's theoretical framework defines the metaparadigms of nursing as: (a) the client as an open system; (b) health as a continuum of wellness; (c) nursing as an inimitable profession concerned with all variables impinging on an individual; and (d) environment as all the internal and external circumstances enveloping the client structure (Freese & Lawson, 2010). Neuman's theoretical structure is comprised of two major constituents: stress and methodical, or systematic, feedback loops (Freese & Lawson, 2010). In this way, the patient, or client, "…is an open system in which continual cycles of input, processing, output, and feedback make up an active organizational pattern" (Butts & Rich, 2010, p. 423).

According to Neuman's theoretical framework, the patient, or client, resides at the core of the nursing model and is surrounded by lines of defense and resistance. In this literature review, the obese client, or a client with an altered gut microbiome will occupy this core. The lines of defense will be represented by primary, secondary, and tertiary prevention strategies, as well as the identification of stressors coming into contact with the lines of defense. The health state of the client system will be dependent on the degree of reaction within clients' system, and the interventions enacted by the healthcare

provider. According to Neuman's model, the client suffers illness or disease when the lines of defense and resistance are compromised, and the individual can no longer maintain homeostasis. In this literature review, the threat to homeostasis will be inappropriate antibiotic prescriptions. When there are compromises in the lines of defense and resistance, and a threat to homeostasis is considered, nurse practitioner interventions are required in order to allow the reconstitution of the lines and bring about homeostasis. Ultimately, the use of the Neuman's Systems Model can potentially identify the nurse practitioner's action of ordering an antibiotic for a client as helpful or harmful, thus theoretically associating a distorted microbiome as a contributory factor in obesity.

PICO Question

The rates of obesity continue to increase despite the advancement of science, technology, and healthcare. Corpulence is not a simple question of an imbalance of calories in verses calories out, but is a multifaceted disease with numerous causes. In an effort to address a portion of this complexity comes the query, does the microbiome of the human gut occupy a niche in the obesity epidemic?

Review of Literature

A review of the literature was conducted from 2011 until 2016 from the following databases: NIH Human Microbiome Project, PLoS One, ClinicalKey, CINAHL complete, and Medline. Selected articles in the review of literature had to meet particular criteria prerequisites to be included. These criteria included a publish date within the previous five years, peer examined articles, full text availability at the database being searched, and be available in the English language. This review of literature took place between the months of May to December of 2016. The inquiry included the following

key words and headings: microbiome, bacteria and obesity, gut bacteria, perturbation of microbiota, antibiotics and obesity, commensal bacteria, sub-therapeutic antibiotic therapy, brain-gut-axis or BGA, microbiota-gut-brain axis or MGB axis, and human microbiome project. Searched information was limited to literature reviews, comprehensive reviews, systematic reviews, and clinical trials. An extended search was carried out utilizing the National Institute of Health, the Centers for Disease Control, the Food and Drug Administration, and Up-To-Date, as well as medical textbooks and non-fiction science books. A total of one hundred and thirteen results were obtained, of which twenty were chosen based on the information acquired from the abstracts provided with the articles.

Categories

Microbial Convergences of the Human

The origin of microbial residency coincides with the birth of a human fetus. This simultaneous cohabitation of human and bacterial cells takes place along the traditional pathway, the vagina. As uterine contractions propel the fetus towards a hostile environment he or she is encased in a moist covering of vaginal microbes. During the birthing process no fetal body surface area is devoid of exposure. The infant's eyes, nose, mouth, and skin are all equally subjected. Later, as the baby emerges, normally face down, he or she is exposed to the maternal fecal microbes (Collen, 2015). Alternately, the widespread use of caesarean section introduces the infant to the potentially pathogenic maternal microbial communities of the skin, as well as pathogenic microbial communities of the procedural environment (Chu et al., 2016). The process of childbirth constitutes the initial encounter of the infant with microorganisms capable of colonizing the infant's

intestinal tract, and sets the stage life-long co-habitation (Madan et al., 2016). Who, or what, are these bacterial cells, which establish this potentially interdependent relationship?

A study by Ravel et al. (2011) was performed in order to ascertain the vaginal microbiome of reproduction-age women. This population based cohort study consisted of four ethnic backgrounds; Caucasian, Black, Hispanic, and Asian, totaling 396 North American women. The researchers had each female to collect mid-vaginal samples utilizing two swabs. One swab was utilized to evaluate the vaginal microbial communities on the basis of the Nugent criteria to diagnose bacterial vaginosis, and one swab was employed to determine the vaginal microbial species composition (Ravel et al., 2011).

Bacterial culturing was not employed. Instead, whole bacterial genomic DNA was mined, and the bacterial genome was sequenced utilizing 16S rRNA pyrosequencing. A total of 282 taxa were observed in the vaginal microbiota. The study by Ravel et al. identified five major microbial communities and designated them as I, II, III, IV, and V with 104, 25, 135, 108, and 21 taxa respectively. Group I communities were dominated by *Lactobacillus crispitans*. Group II, III, and V communities were dominated by *Lactobacillus gasseri*, *L. iners*, and *L. jensenii*. The study found that group IV was the most diverse and was dominated by *Prevotella*, *Sneathia*, *Megasphera*, and *Streptococcus*, all genera known to produce lactic acid. Vaginal bacterial groups dominated by *Lactobacillus*, groups I, II, III, and V, were found in 80.2% of Asian and Caucasian women, but only 59.6% and 61.9% in Hispanic and Black women. The

individuals with vaginal bacterial communities not dominated by *Lactobacillus* were predominately Black and Hispanic women (Ravel et al., 2011).

The study by Ravel et al. highlighted the differences of the various ethnic groups in terms of what is considered a normal microbial community. This study identifies no core microbiome for the human vagina, and the ratios of each microbial group varied among the ethnic groups and were statistically significant, $p < .0001$ (Ravel et al. 2011). Not only are there large numbers of various ethnicities, but also a diversity in relation to the human vaginal microbiome housed with each individual within the ethnic group. Understanding the various compositions of vaginal microbial communities allows the practitioner to comprehend the probability that the maternal microbiome is hereditary.

A study by Madan et al. (2016) was conducted to observe the correlations of delivery mode and feeding method with newborn intestinal microbiome structure at approximately six-weeks of life. This longitudinal cohort study consisted of 102 infants, which 70 were delivered vaginally, and 32 were delivered by cesarean section. Additionally, 70 infants were exclusively breast-fed, 26 infants received a combination of breast milk and formula, and six infants were fed exclusively formula (Madan et al., 2016).

The results of this study highlighted five statistically significant findings. The first finding was that the delivery mode was strongly associated with the infant's gut microbiome composition, $p < .001$. Secondly, there is a strong association between feeding method and the infant's stool microbial community composition, $p < .001$. Thirdly, the infants fed exclusively by breast milk had microbial communities distinctly different from the other feeding modalities, $p < .04$. Fourthly, there was no statistically

significant difference in the microbiome composition of infants fed either exclusively formula or a combination of formula and breast milk. Finally, vaginal delivery was associated with an increased abundance of the *Bacteroides* and *Bifidobacterium* taxa, and a decrease in the *Staphylococcus* taxa versus cesarean delivery, $p < .001$ (Madan et al, 2016).

The importance of these findings can be overlooked at first blush. There is a well-established bond between breast-feeding and a lower probability for youth and adult-onset obesity (Madan et al., 2016). Studies have validated this correlation, which is mediated in part by the microbiome in early life (Madan et al., 2016). This mediation is through the maternal production of oligosaccharides present in breast milk (Madan et al., 2016). The oligosaccharides, in turn, promote *Bifidobacterium* growth in the infant's intestines. A decreased abundance of *Bifidobacterium* in infancy has been found to be concomitant with an increased risk for being overweight at age 10 (Madan et al., 2016). Thus, a vaginally delivered and exclusively breast-fed infant has the increased probability of not becoming obese in later life.

To determine if the maternal diet affects the neonatal microbiome, Chu et al. (2016) conducted a longitudinal cohort study. The cohort study was conducted to establish the possibility that a high-fat maternal diet could impact the infant's intestinal microbiome. Chu et al. prospectively enrolled 163 women during their third trimester and the intra-partum period. A subgroup of 81 maternal-neonate pairs consented to longitudinal sampling from the post-partum period through six-weeks. In order to determine maternal dietary patterns the Dietary Screener Questionnaire (DSQ), developed by the National Health and Examination Survey (NHANES), was utilized

(Chu et al., 2016). After the questionnaires were scrutinized, the cohort was further subdivided into two smaller groups. One group, the control group, consisted of 13 participants who consumed a low-fat diet. The other group of 13 participants consumed a high-fat diet. To determine the infants' microbiome, the meconium stool samples were collected at 24-48 hours after delivery and again at six-weeks of age (Chu et al., 2016).

The results of the study revealed that 103 bacterial taxa were identified in the meconium despite the short exposure time to the maternal and environmental bacterial communities. Gene sequencing of the bacterial DNA within neonatal meconium uncovered a relative depletion of the *Bacteroides* taxa, which was correlated with a high-fat diet during gestation. The stool samples collected at the six-week mark revealed that exposure to a maternal high-fat diet was significantly associated with an abundance of the *Enterococcus* taxa and a relative reduction of the *Bacteroides* taxa (Chu et al., 2016).

The correlation between a maternal high-fat diet and the infants' microbiome composition after delivery is not surprising, but a high-fat diet during gestation causing an altered gut microbiome in the infant is unanticipated. The researchers compared the meconium bacterial samples with those collected at six-weeks of age and found that there were significant differences at the phylum level. The researchers concluded that this finding represents a broad rearrangement of the gut microbiota during this period of time (Chu et al., 2016). Further, it is hypothesized that an increased consumption of animal proteins persistently altered the continuum of commensal bacteria indigenous to the digestive tract, namely *Bacteroides fragilis* (Chu et al., 2016). *Bacteroides fragilis* is inherited from maternal fecal material during natural childbirth, and its colonization in early life is correlated with a lower body mass index in later life (Chu et al., 2016).

A longitudinal cohort study was conducted to evaluate the associations between caesarean delivery and child body mass (Blustein et al., 2013). The study enrolled 10,219 children born from 1991 to 1992; of these children, 926 were delivered by caesarean section. These children were followed from the age of six weeks until 15 years of age.

This study found that infants born via caesarean section had lower birth weights than those born vaginally. Interestingly, in the study's mixed multivariable models, when adjusting for birth weight, socio-demographics, gestational factors, and feeding patterns the children born via caesarean section were consistently associated with increased adiposity (Blustein et al., 2013). This increase of adiposity began at six-weeks of age and continued through age 15 (Blustein et al., 2013). Also, caesarean delivered children had 1.83 times the odds of increased adiposity and obesity as their vaginally delivered counterparts (Blustein et al., 2013).

These findings support the hypothesis of caesarean delivered children exhibiting a microbial dysbiosis resulting from bacterial colonization from maternal skin and the procedural environment, which has been associated with a delayed *Bacteroides* colonization in early life (Chu et al., 2016) Alternatively, children born vaginally were generally the least likely to develop obesity. This corresponds to the likelihood that vaginally born children are exposed to the maternal vaginal, and to an extent the maternal fecal, microbiome during birth, and thus later life adiposity is reduced (Chu et al., 2016). An observed weakness of this study is in the fact that the researchers did not sample the subject's intestinal microbial communities to ascertain any differences in the caesarean delivered children versus those vaginally delivered.

Early life is a precarious period for the microbial colonization of the infant's intestinal tract. The early microbial colonization of the human can be altered by delivery methods, infant feeding practices, and the maternal diet. One other mechanism can interrupt, or disrupt the infant's gut colonization by commensal bacteria and that mechanism is early antibiotic introduction.

Trasande, Blustein, Liu, Corwin, Cox, & Blaser (2013) conducted a longitudinal birth cohort study of 11,532 children born in Avon, UK. This particular study was part of a much larger study named the Avon Longitudinal Study of Parents and Children (ALSPAC). Their study examined the influence of infant antibiotic contact and its impact on early life adiposity.

The children were examined at less than six months of age, six to fourteen months of age, and fifteen to twenty-three months of age. Children who were exposed to antibiotics before the age of six months were at significantly greater odds of being overweight at 38 months and at seven years of age (Trasande et al., 2013). When maternal weight was analyzed, infants with mothers at a normal weight experienced greater effects. These infants, when exposed to antibiotics before six months of age had a 29.4% increase in overweight (Trasande et al., 2013).

This study highlights and reinforces the concerns regarding infant antibiotic exposure. The vulnerable period for the infant is before the age of six months. There are limitations to this study as the results can be confounded by social, environmental, and biological factors. One simple social factor to be taken into account is the ability of the mother to have adequate memory recall of the infant's antibiotic use.

Microbial Interaction with the Human Host

The human, and his or her microbiome, comprises a thought-provoking relationship a symbiotic relationship that lasts the humans' entire lifespan. This conglomeration of human and microbial cells constitutes what can be termed as a super-organism. The human super-organism is comprised of over 100 trillion cells, and each of these cells contains genetic material (Cantarel, Lombard, & Henrissat, 2012). The estimated number of microbial genes, housed just within the human gut, is approximately 3.3 million, while the entirety of the human genome consists of only 19,000 to 20,000 genes (Slyepchenko et al., 2016). A revelation comes with the knowledge that the microbial cells outnumber the human host cells by a factor of ten to one (Dominianni et al., 2015). This extraordinarily large disparity between human and microbial cells, and human and microbial genomes raises the question, do the bacterial cells influence the human host?

In 2016, Slyepchenko et al. authored a systematic review of the literature. The review was conducted to explore the role of an altered gut microbiome and its relationship to major depressive disorder, obesity, and type 2 diabetes. A total of 207 articles from PubMed and MEDLINE searches were examined. The outcome of this study begins with how bacterial cells interact with the human host.

Normally, 90% of the intestinal microbial community is made up of *Bacteroidetes* and *Firmicutes* and is often expressed as a ratio (Slyepchenko et al., 2016). When there is an intestinal microbial dysbiosis, the ratio of *Bacteroides* to *Firmicutes* is altered, and *Firmicutes* and other sub-dominant phyla can then exert their influence (Slyepchenko et al., 2016). The review points out that the diet sculpts the structure of the gut microbiome

throughout the human lifespan (Slyepchenko et al., 2016). The increase in dietary high-fat foods can result in an altered gut microbiome and contribute to a vicious cycle of low-grade inflammation and weight gain. Thus, obesity has an underlying pathophysiology of chronic low-grade inflammation brought about, in part, by the gut bacteria.

The reduction in the *Bacteroidetes* phyla, as a result of high-fat dietary intake, results in a decrease in the production of butyrate. Butyrate is a short chain fatty acid that is responsible for preserving mucin production in the colon, sustaining tight epithelial junctions within the intestines, tempering intestinal epithelial proliferation, and the inhibition of NF-KB, which by the inhibition supports intestinal barrier integrity (Slyepchenko et al., 2016). The reduction in the abundance of *Bacteroidetes* allows for an increased incidence of the translocation of bacterial cells, bacterial chemokines, and bacterial genetic material through the intestinal epithelial matrix junctions and into the host circulation (Slyepchenko et al., 2016).

The incursion of bacterial products into host circulation inaugurates the inflammatory cycle. The numerous chemokines in circulation within the obese individual, as a direct consequence of an altered gut microbiome, includes: IL-1B, IL-6, C-reactive protein, soluble IL-2 receptor, TNF-alpha, plasminogen activator inhibitor, and serum amyloid A (Slyepchenko et al., 2016). Also of importance, are the obese individuals' elevated serum levels of lipopolysaccharides. Lipopolysaccharides (LPS) are the components of bacterial cell walls and directly lead to adipose tissue inflammation (Slyepchenko et al., 2016).

The mechanisms by which bacteria exert their influence on the human have not been fully elucidated, but numerous concerted efforts have taken place. To examine the

link between the gut microbiota and adipose tissue inflammation Pekkala et al. conducted a longitudinal cohort study published in 2015. The cohort consisted of eight women recruited from the Finnish Academy SKID-KID program (Pekkala et al., 2015).

The study examined Toll-like receptors (TLR) of the cohort's participants. Participants were grouped according to having either low TLR5-signaling pathway genes (L-TLR), or those with high TLR5-signaling pathway genes (H-TLR). There were four participants in each group. The H-TLR participants were heavier, had higher body mass indices, greater waist circumferences, higher systolic blood pressures, and elevated serum levels of leptin, LDL, and triglycerides (Pekkala et al., 2015). The H-TLR groups' abdominal adipose tissue biopsies revealed their genome had 419 up-regulated and 249 down-regulated genes directly related to altered metabolism and increased inflammation (Pekkala et al., 2015).

The H-TLR group had a recognizable intestinal dysbiosis that was statistically significant (Pekkala et al., 2015). The dysbiosis was seen as a higher *Firmicutes* to *Bacteroidetes* ratio, higher sub-phyla abundances of flagellated *Clostridium*, and lower *Bifidobacteria*. The resultant dysbiosis lead to translocation of bacterial products into host circulation. The inflammatory process ensues from the lipopolysaccharides activating the TLR5 pathway, and as a direct consequence leads to adipose tissue hypertrophy and macrophage infiltration into adipose tissue (Pekkala, et al., 2015). Interestingly, the study uncovered evidence that the simple ingestion of a high-fat diet resulted in TLR1, 5, 8, 9, and 12 pathways being over-expressed in the visceral adipose tissue (Pekkala et al., 2015). One other caveat, the study highlighted the consequences of the increased abundances of a sub-phylum, such as *Clostridium*. *Clostridia* are short

chain fatty acid (SCFA) producers, and as a result, these bacteria increase the total number of calories extracted from undigested foods and increase lipogenesis. In short, these bacteria contribute to energy harvesting and increase the serum lipids for their human host (Pekkala et al., 1015).

In the framework of gut barrier integrity, a high-fat dietary intake can cause epithelial disruption and intensify intestinal permeability. Lau et al. (2016) examined the function of intestinal fatty acid binding protein (I-FABP) as a potential biological marker of intestinal barrier dysfunction. The study subjects were 12 Wistar rats randomly divided into two groups of six. One group was fed a standard diet (SD), and the second group was fed a high-fat diet (HF). The rats were utilized because their gut microbiota is similar to humans (Lau et al., 2016).

The results confirm earlier studies and are statistically significant, $p < 0.05$. The HF group had lower *Bacteroides* taxa and a higher *Firmicutes* to *Bacteroides* ratios. The *Firmicutes* to *Bacteroides* ratio was positively correlated with weight gain the HF group. As a consequence of the HF diet and higher *Firmicute* abundances the intestinal barrier function was diminished. Serum lipopolysaccharides (LPS) were elevated in the HF group and were positively correlated with the increased abundance of *Firmicutes* (Lau et al., 2016). The high-fat diets caused obesity, and as a result, triggered a dysbiosis of the rats' intestinal gut microbiome. The resulting dysbiosis increased the host's TLR4 pathway gene expressions and contributed to the increase in LPS causing higher circulating pro-inflammatory chemokines (Lau et al., 2016). The hypothesis put forth by this study suggests that a high-fat diet up-regulates genes known to enhance SCFA

synthesis and uptake, and promote chronic low-grade inflammation via gut microbiome manipulation (Lau et al., 2016).

The distorted gut microbial populations of the obese can impact the host in seemingly innocuous ways when viewed on the macro-scale. When viewed on the micro-scale, the gut microbiome responds to the hosts' preferences in food choices, and as a result, these food choices initiate a cascade of changes to the host. These changes include: increasing adiposity deposits, alterations in host energy scavenging, deregulation of the intestinal barrier function, and shifting the composition of the dominant phyla within the hosts' gut. Ravussin et al. (2012) conducted a randomized controlled trial to investigate the impact of a 20% reduction in weight on the gut microbiota of diet-induced obese mice. The study was conducted to reveal any responses of the obese mice's intestinal bacteria to diet composition and weight loss.

The researchers divided 32 mice randomly into four groups of eight. The groups were then fed a controlled diet, and labeled as diet induced obese mice, control diet fed mice, weight-reduced to 20% below initial weight mice, and weight-reduced control diet mice (Ravussin et al., 2012). The results specify that different diets foster diverse bacterial communities, and that weight reduction modifies the gut microbial community of diet induced obese mice, but not of mice fed a control diet (Ravussin et al., 2012). More specifically, the diet induced obese mice had higher abundances of *Firmicutes,* and a significant reduction in the circulating host serum leptin levels (Ravussin et al., 2012). The act of consuming a high-fat diet leads to a change in dominant bacterial phyla within the hosts' gut, and is not related to the caloric intake (Ravussin et al., 2012). The serum leptin levels were highly correlated to total fat mass and circulating leptin levels declined

approximately 80% in the diet induced obese mice when compared to the control fed mice.

The study established that the gut microbiota influence the host through the translocation of bacterial products via the disrupted intestinal epithelial barrier. The translocation of bacterial products, namely lipopolysaccharides, induces a chronic low-grade inflammatory cycle evident in white adipose tissue gene expression (Ravussin et al., 2012). The study acknowledged that the host microbiota would contribute to host adiposity through energy harvesting. Energy harvesting takes place in the large intestines via microbial breakdown of undigested complex polysaccharides and increased production of SCFA (Ravussin et al., 2012). This process, in turn, gives the host an increase in total caloric and fatty acid intake (Ravussin et al., 2012).

Shoaie et al. (2013) conducted a descriptive correlational study aimed at identifying the relations between the human microbiota through metabolic modeling. Three genome-scale metabolic models were utilized, which represent the three most common phyla of microbial life in the human intestine. These microbes include: *Bacteroides thetaiotamicron, Eubacterium rectale,* and *Methanobrevibacter smithii* (Shoaie et al. 2013). These organisms are more commonly referred to as *Bacteroides, Firmicutes,* and *Archaea*. Interestingly, this study was carried out via mathematical models, super-computer simulations, and genomic algorithms.

The mathematical model predictions identified increased SCFA production that was correlated with the increased abundances of the *Firmicute, Eubacterium rectale* (Shoaie et al., 2013). The production of butyrate, a SCFA, increased when *Bacteroides thetaiotamicron* was co-colonized with *Eubacterium rectale*. The increased production

of this SCFA is associated with colon cancer, diabetes, and obesity (Shoaie et al., 2013). The mathematical model also discovered that the hosts' glutamine was taken up by *E. rectale* and converted to glutamate. This increased utilization of glutamine by the *Firmicutes* results in decreased serum levels of this nitrogenous product correlating with increased incidences for diabetes and metabolic syndrome for the host (Shoaie et al., 2013).

The Microbiota's Contribution to Obesity

Studies in mice and humans specify that the intestinal microbiome change both sides of the energy-balance calculations by promoting nutrient absorption and regulating host gene expression altering adiposity. There remains an ambiguity as to what extent the intestinal microbiota regulates nutrient absorption in humans. Jumpertz et al. (2011) conducted a single randomized clinical trial examining how the gut microbial community arrangement is affected by the nutrient load.

Twelve lean individuals with a body mass index of 18.5 to 24.9 and nine obese individuals with a body mass index of greater than 30 were randomly assigned a 2400-kcal diet or a 3400-kcal diet (Jumpertz et al., (2011). Fecal samples were taken before and at scheduled intervals during the experiment. The *Bacteroides* and *Firmicutes* represented 97% of the sequenced genomes (Jumpertz et al., 2011). The prevailing class-level representatives of the *Bacteroides* and *Firmicutes* were *Bacteroidetes* and *Clostridia,* and this representation was irrespective of the experimental diet (Jumpertz et al., 2011).

The results of the nine-day experiment were noteworthy. The researchers not only looked at the various bacterial genomes, but also the caloric loss experienced through the

expulsion of stool. The lean subjects lost relatively less energy in stools with the 3400-kcal diet than with the 2400-kcal diet (Jumpertz et al., 2011). Also, the lean subjects assigned the high caloric intake experienced rapid phylum level changes after only three days (Jumpertz et al., 2011). A 20% increase in the abundances of the *Firmicutes* was noted in the high caloric intake of the lean and obese subjects, and an increased nutrient absorption of approximately 150-kcal per day (Jumpertz et al., 2011). The increased nutrient load induced rapid changes in the gut microbial communities and hints at the possibility that the microbiome senses the alterations in the nutrient availability and subsequently modulates the hosts' absorptive capabilities.

Semova et al. (2012) examined how the gut microbiota and dietary fat intake interact to regulate lipid absorption in the intestinal epithelium. Zebra fish larvae were randomly assigned to be incubated conventionally or as germ-free. The researchers "…developed a method to monitor fatty acid absorption into the gut epithelium by incubating the fish in liposomes containing fatty acid analogs that are fluorescently labeled" (Semova et al., 2013). The fish were used due to their digestive tract physiology and anatomy, and their lipid metabolism being analogous to mammals and other vertebrates.

The outcomes of this study ascertains that the colonization of the gut by bacteria promotes epithelial absorption of fatty acids and results in the accumulation of lipid droplets in the enterocytes and extra-intestinal tissues (Semova et al., 2013). Furthermore, the phyla of *Firmicutes* were developed in the intestines of fed fish, where they augmented the proficiency of the host enterocytes to absorb fatty acids (Semova et al.,

2013). As a result, the amplified abundance of *Firmicutes* is positively correlated with dietary intake.

Wu et al. (2011) organized a quasi-experimental randomized clinical trial in an effort to associate long-standing dietary models with gut microbial ecosystems. The experiment had a ten-day duration and consisted of ten participants who were randomly selected from a pool of 98 healthy potential subjects (Wu et al., 2011). The participants were segregated in a hospital setting and were randomly selected to consume one of two diet types. One diet type included a high fat, low fiber diet, while the other diet consisted of low fat and high fiber (Wu et al., 2011). Stool samples were collected at the onset and at predetermined intervals during the study.

The results were similar to other previous study outcomes. The ten participants, at the onset, exhibited predominately a *Bacteroides* phyla within their respective intestinal microbial ecosystems, while only one self-reported vegan displayed a *Prevotella* phyla (Wu et al., 2011). There were no reported abundances of *Firmicutes*. During the controlled feeding study the group consuming the high fat low fiber diet had significant microbial ecosystem perturbation within the initial 24 hours of the study (Wu et al., 2011). Despite the initial distress, the dominant phyla within the respective microbial ecosystems did not succumb to sub-phlya population excursions (Wu et al., 2011). Notably, the study identifies nutrients from fat versus plant products and fiber to exhibit an inverse association with the microbial taxa (Wu et al., 2011). The hypothesis, put forth, was only the hosts' long-term diet choices would cause a significant change to microbial ecosystem domination from one phyla to another.

A human's intestinal microbiome consists of more than bacteria. The microbiota contains bacteria, archaea, viruses, yeasts, fungi, and bacteriophage products. A relationship exists between archaea, fungi, and bacteria. These microbial species form a symbiotic population, in which the metabolic waste from one microbe provides nutrients for another. Thus, other constituents may alter a human's microbial ecosystem. Hoffman et al. (2013) carried out a longitudinal cohort study to identify the archaea and fungi of the human gut microbiome and relate them to the diet and the bacterial occupants. Ninety-eight healthy participants completed dietary inventories with the Willett food frequency questionnaire, and provided stool samples for 16S rRNA gene sequencing (Hoffman et al., 2013).

All fecal samples tested positive for at least one archaeal genera with 44 of the 96 samples having five archaeal genera (Hoffman et al., 2013). All fecal samples produced fungal sequences with a detection of 66 known genera and 16 uncategorized genera (Hoffman et al., 2013). The most common archaea were *Methanobrevibacter* and *Nitrososphaera*, and the most common fungi were *Saccharomyces, Candida*, and *Cladosporium* (Hoffman et al., 2013). Three microbial genera were identified with a high proportional intake of carbohydrates, and these were *Methanobrevibacter, Prevotella*, and *Candida* (Hoffman et al., 2013). The study identifies *Candida* as having the ability to degrade undigested carbohydrates to liberate simple sugars, which in turn are fermented by bacteria and absorbed by the host, thereby contributing to energy harvesting.

Obesity is not a transient condition, but is a chronic disease process marked by persistent high calorie intake and an abnormal intestinal microbial ecosystem. Obese individuals have been shown to have an altered *Bacteroides* to *Firmicutes* ratio as a result

of high fat dietary choices (Lau et al., 2016). The dietary preferences of the human host play a pivotal role in the intestinal microbial community composition with changes occurring in as early as 24 hours (Wu et al., 2011). This raises the question; can chronic dysbiosis be remedied by the initiation of long-term dietary changes? Simoes et al. (2014) managed a longitudinal cohort study to consider the influence of a low energy diet on the intestinal microbiota of obese participants. The cohort consisted of 16 obese participants who consumed a very low energy diet (VLED) for six weeks, followed up after five, eight, and twelve months, and submitted fecal samples at predetermined intervals throughout the study (Simoes et al., 2014). In addition, the six males and ten females participated in individual and group exercise and lifestyle counseling (Simoes et al., 2014).

The bacterial phyla in the greatest abundance among the obese participants at the baseline included: *Clostridial clusters XIVa, XIVb,* and *IX*, *Faecalibacterium prauznitzii*, and *Bifidobacteria* (Simoes et al., 2014). It was not until the end of the six-week VLED period that there were significant reductions in *Clostridia*, *Bifidobacteria*, and *Lactobacillus* and significant increases in the sub-phyla of *Bacteroides* among the obese participants (Simoes et al., 2014). It was hypothesized that the reduction in carbohydrate intake reduced the substrates available to *Bifidobacteria* and *Lactobacillus*, thereby decreasing SCFA production. Also, the reduction of the *Clostridia* phyla decreased total energy harvesting (Simoes et al., 2014). The conclusion of the study, after twelve months, resulted in an average weight loss of nine kilograms and a total decrease in energy intake by 64.6% (Simoes et al., 2014). Also, at the conclusion of the study, all bacterial phyla groups tended to increase except for *Bacteroides* (Simoes et al., 2014). This could

indicate that the participants may have reverted back to their familiar and common foods consumed prior to the study's initiation. Ultimately, the cohort study corroborates the notion that an alteration of the dietary intake provokes changes in the intestinal microbial ecosystems.

One of the most abundant food and nutrient sources includes simple and complex carbohydrates. Human digestive enzymes are capable of degrading simple carbohydrates, but are unable to breakdown the majority of the complex carbohydrates found in most plant based foods. The complex cellular structures of most plant cell walls do not lend themselves readily to enzymatic breakdown. Cantarel, Lombard, & Henrissat (2012) conducted a longitudinal cohort study with 148 participants to examine how complex carbohydrates are degraded by bacteria in the human gut. The categorized human genome data were analyzed and the microbial gene sequences were considered in relation to complex carbohydrate utilization.

The 148 participants collected bacterial samples from five different body sites including the stool. A total of 520 samples were analyzed utilizing shotgun metagenomics and 16S rRNA sequencing of the bacterial genome (Cantarel et al., 2012). After data processing, it was revealed that the human genome only encodes for 97 glycoside hydrolases (GH) with only 17 known enzymes existing for carbohydrate breakdown (Cantarel et al., 2012). Conversely, one bacteria species alone, *Bacteroides thetaiotaomicron* encodes 260 glycoside hydrolases (GH) for carbohydrate breakdown (Cantarel et al., 2012). The oral samples collected provided bacterial samples yielding bacteria capable of enzymatic degradation of carbohydrates. No longer is salivary amylase the only enzyme available for initial carbohydrate digestion. The bacterial

enzymes contained within the oral cavity include: GH6, GH26, GH28, and GH43 (Cantarel et al., 2012). Notably, these enzymes are nonexistent in the human genome (Cantarel et al., 2012). It was observed that the human microbiome is more specialized in the area of carbohydrate metabolism than that of animal protein or animal carbohydrate (Cantarel et al., 2012).

Multiple variables must be taken into account when looking at the intestinal microbiome. The diet, antibiotic exposure, logistics, birth method, and early life bacterial exposures are all factors of what constitutes the intestinal microbial community. Dominianni et al. (2015) explored another avenue. Dominianni et al. studied 82 participants to identify a correlation between gender, body mass index, and dietary fiber intake with the intestinal microbiome.

There were 51 men and 31 women comprising this study, and it was found that women had significantly different intestinal microbial compositions overall (Dominianni et al., 2015). Women in general had lower populations of *Bacteroides* than men, especially those female individuals who were obese (Dominianni et al., 2015). The hypothesis was that estrogen might play a role in gut microbial populations. These findings were congruent with earlier studies, which identified lower *Bacteroides* populations in obese versus normal weight female twins (Turnbaugh et al., 2009 & Dominianni et al., 2015). Adipose tissue is not an inert substance, but an active organ with endocrine excreting qualities. Once such product of adipose tissue is estrogen. This study identifies that obesity decreases the *Bacteroides*, but so too does higher serum levels of estrogen (Dominianni et al., 2015). Thus, the body mass index could be a

mediating factor as the increasing adiposity modulates the gut microbiome though estrogen production.

Kulecka et al. (2016) conducted a randomized controlled trial utilizing 48 male mice. The study considered the modifications of the gut microbiota under long-term contact with a high-fat diet. Mice are utilized due to the similarities of the human and mouse intestinal microbiota (Kulecka et al. 2016). The mice were randomly selected and sequestered into three groups of 16. One group was fed a normal diet (ND), one group was fed a high-fat diet (HFD), and one group was fed a high-fat diet supplemented with feces from the ND mice (HFDS).

After data processing, the most abundant bacterial phyla at the onset of the study was the *Bacteroidetes* with 70.6%, *Firmicutes* with 22.5%, and *Proteobacteria* with 4.8% of the bacteria population (Kulecka et al., 2016). After the twelfth week, both HFD and HFDS mice were obese and exhibited significant increases in the abundances of *Firmicutes* and *Actinobacteria*, more commonly known as *Clostridia* and *Bifidobacteria* (Kulecka et al., 2016). Interestingly, obesity in the mice was associated with an increase in both *Bacteroidetes* and *Firmicutes*, and persistent conveyance of the ND gut bacteria to the HFD mice hastened the onset of obesity and augmented adiposity (Kulecka et al., 2016).

Kong et al. (2013) conducted a longitudinal cohort study of 30 obese women enrolled in a bariatric surgery program. The study was conducted to ascertain the probability of gut microbial changes after a Roux-en-Y gastric bypass procedure. Of the 30 participants, seven were diabetic and 23 were non-diabetic. Stool samples were collected at the initiation of the study and at predetermined intervals after the procedure

(Kong et al., 2013). Periumbilical adipose tissue samples were acquired at commencement and three months post-procedure (Kong et al., 2013). Genetic studies were carried out utilizing 16S rRNA sequencing for bacterial identification and Agilent 2100 Bioanalyzer for human adipose samples (Kong et al., 2013).

Upon completion of the study, it was revealed that 58 bacterial genera that had been undetectable before the gastric bypass were detected three months post-procedure (Kong et al., 2013). These previously undetected genera were transient species from the periodontal and oropharyngeal ecosystems. Intestinal bacterial phyla that increased after the gastric bypass included *Bacteroides, Alistipes,* and *Proteobacteria*. The phyla that decreased after the procedure included *Firmicutes* and *Actinobacteria* (Kong et al., 2013). The most notable data concerns the gene expression exhibited in the white adipose tissue samples. The study revealed 153 white adipose tissue genes, garnered from adipose tissue sampling, which revealed human gene expression was associated with at least one bacterial species (Kong et al., 2013). This alludes to the fact that the bacteria may influence human gene expression.

Walters, Xu, & Knight conducted a meta-analyses of available microbial associated obesity literature. The researchers examined data compiled using the QIIME database. The QIIME database is a repository for genetic based studies relating to the microbiome (Walters, Xu, & Knight, 2013). The analysis reveals that the microbial communities within the human are not the sole contributors to obesity, but alterations in the intestinal microbiome are observed in obese humans (Walters et al., 2013). Moreover, significant microbial differences are apparent and the ability to classify individuals as obese or lean based on dominant bacterial phyla has a 90% accuracy rate (Walters et al.,

2013). Studies promoting one bacterial phyla over another have resulted in contradictory results. Many studies identify an increased *Firmicutes* to *Bacteroides* ratio as a sign of dysbiosis within the human gut, but other studies may show no tendency, or even an opposite inclination (Walters et al., 2013). The study by Walters, Xu, and Knight compared the means of the ratios for subjects with a normal versus an obese body mass index and in all studies but one there was a tendency showing an increased *Firmicutes* to *Bacteroides* ratio. Conversely, no significant disparities between obese and lean subjects were found using Wilcoxon rank sums tests, nor was the variance in *Firmicutes* to *Bacteroides* ratio statistically significant using Fisher's Method for combining multiple independent tests of a hypothesis (Walters et al., 2013).

Obese individuals have been described as having a less diverse intestinal microbiome than normal weight individuals, but the results of this meta-analysis imply that the density of a bacterial community does not commonly differentiate these communities (Walters et al., 2013). As a result, the study outcomes are much larger than the biological influences separating the lean from the obese human, and herald the need for more regulation of variables among the studies (Walters et al., 2013).

Summary of the Literature

The gut microbiota communally act as a metabolic structure supplying resources for themselves and for the host they populate (Cantarel et al., 2012). How the human acquires this symbiotic bond is dependent on the mother's gestational diet, birthing method, and feeding practices and is in a continual state of flux throughout the lifespan (Madan et al., 2016; Chu et al., 2016; & Blustein et al., 2013). Moreover, in the infant to childhood timeframe, how the human cultivates the optimal balance of *Fermicutes* to

Bacteroides ratio is dependent on the avoidance of early life antibiotic exposures (Trasande et al., 2013 & Lau et al., 2016). The avoidance of unnecessary early life antibiotic exposures assists the growth and development of not only the human, but the microbiome as well. As the human, and their microbiome, grows and matures, the process of maintaining low fat, high fiber dietary choices is paramount to the overall health of each (Dominianni et al., 2015).

We live in a mutual coexistence with our gut microbiota, but this affiliation occasionally becomes pathological, such as in obesity (Wu et al., 2011). The prevailing wisdom has been grounded on evidence that an increase in caloric intake coupled with a decrease in physical activity results in weight gain (Simoes et al., 2014). While this is true, it is not solitary dogma. There is evidence, which directs towards an environmental factor in the obesity epidemic. This environmental factor involves the increased energy harvesting capabilities by the intestinal bacteria promoting greater caloric availability to the host, thus allowing for prodigious adiposity stores (Simoes et al., 2014). Also, research has elucidated that obesity is associated with, and results in, phylum level changes in the intestinal microbial populations, an alteration of bacterial and human gene expressions and their respective metabolic pathways, and a diminished intestinal microbial diversity (Turnbaugh et al., 2009). In effort to assist in combating the obesity epidemic, the medical provider can accomplish effective mediation through education on the microscopic co-inhabitants. Not surprisingly, this education includes: increasing the number of vaginal deliveries, reinforcing the need for breast feeding, decreasing unnecessary antibiotic administrations, adopting a long-term low fat, high fiber dietary choices, and committing to long-term regular exercise.

Limitations

The limitations to this literature review are noteworthy to the nurse practitioner. Firstly, many of the available research studies utilized small sample sizes. The consequence to small sample sizes is the difficulty in finding significant relationships from the data. Secondly, many of the available studies utilize animal models to study the intestinal microbiota. The potential complexities that may arise include human versus animal dissimilarities in gut structure and function, as well as environmental variables. The statistical significance of the data in the animal models studied can be skewed if all pertinent variables are not accounted for. Next, large scale randomized controlled trials from the literature are few. Also, of the large-scale studies conducted, the majority are observational cohort studies where data regarding obesity and the microbiome are inferred. Finally, the precipitous complexity of DNA sampling techniques, genome mapping, and the interpretation of genome data can be daunting. The lack of a substantial background in the sciences of biology and chemistry may, or will limit the nurse practitioner's understanding of the intricacies of intestinal microbe genome data and its potential application to the population.

Recommendations for Advance Practice

In consideration of advanced practice, it is recommended that advanced practice nurses work closely with obese patients in developing educational interventions with long-term goals in mind. Distinctively adapted mediations must be created to fit the needs of each specific patient. It is essential that the advanced practice nurse perform a needs assessment with the patient in order to recognize where education is warranted. One such area includes ongoing patient and community education regarding unnecessary antibiotic

usage. One other method, to ensure an optimal bacterial colonization, is the education on, and the encouragement for, vaginal deliveries. The education and encouragement for a vaginal delivery is not only for the individual, but also with respective medical providers.

When any applicable interventions have been implemented for the patient, the advanced healthcare provider must reassess the patient and establish if successful education is evident. If the long-term interventions are not met, they must be modified to meet the requisites of the patient. The ultimate objective of the education intervention is to allow the patient to make informed decisions regarding birth methods, maternal low-fat diet, restrictive antibiotic usage in the very young, life-long low-fat high fiber dietary choices, and life-long exercise.

Recommendations for Future Research

Future research is obligatory to better understand the microbiome's impact on obesity. This review of literature focused only on three concepts for the advanced practice nurse: how the microbiome is acquired, how the microbiome interacts with the human, and how the microbiome may contribute to obesity. Research should be performed that examines cognitive factors, emotional factors, social factors, developmental factors, and spiritual aspects of the obese patient.

Moving onward, research studies looking specifically at larger sub-sets of the obese population should be conducted, which examines specific geographical areas, cultural tendencies, individual genome mapping, and individualized intestinal microbiome genome identification. Simply put, higher numbers of research studies examining the microbiota and obesity are desirable. This is especially true regarding the

validation of earlier studies, studies utilizing animal models, and studies with very few participants.

Conclusion

The gut microbiota collectively act as a metabolic organ supplying energy for themselves and for the host they inhabit. This symbiotic relationship begins at the onset of a human birth and continues throughout the lifespan. The probability of the microbiota making a contribution to obesity is high. As human beings, we have the capacity to limit the effects of our mutualistic microbial partners, but a change in methodologies is needed. The change requires the human to acknowledge the microbiota as necessary cohabitates, and not an entity to be decimated. Finally, the nurse practitioner can be a trailblazer in this paradigm shift by equating the microbiome to a garden, where the microbes are cultivated and not annihilated. It is not survival of the fittest, but mutual coexistence with a numerically superior force.

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