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The Role of the Gut Microbiome in Autoimmune Disorders

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by

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Abstract

According to the National Institute of Health (NIH), it is estimated that over 24 million Americans are diagnosed with autoimmune disorders, and the cases are increasing (2005). A significant risk factor that has been linked to the formation of these diseases is the gut microbiome. The gut microbiome of the adult plays a vital role in the efficacy of the immune system. The purpose of this research and systematic literature review is to determine how the gut microbiome can influence autoimmune disorders. In this review, five databases were searched including PubMed, DynaMed, Cochrane Library, Embase, and Clinical Key. A variety of keywords and mesh terms were implemented with searching. The search time frame was limited to the previous fifteen years. Inclusion criteria included peer-reviewed journals, meta-analysis, systematic reviews, randomized controlled trials, and case studies. Exclusion criteria originally included animal studies, pediatric, or geriatric focused research. Much of the research presented shows correlations between gut dysbiosis and autoimmune disorders. Although most research does show trending data, no single definitive conclusion has been made regarding the influence of the gut microbiome and its influence on autoimmune diseases. More research still needs to be completed to possibly use gut dysbiosis as a biomarker or possible treatment tool to prevent autoimmune disorders.

Keywords: human microbiome, healthy microbiome, systemic lupus erythematous microbiome, immune function, dysbiosis, leaky gut, and autoimmune disorder microbiome

Introduction

Autoimmune disorders are a grouping of over 80 known chronic disease states. The effects of these illnesses can range from mild disabilities to life-threatening events. In an autoimmune disease, the body will mistakenly mount an attack against its tissues such as joints or even a specific organ by producing antibodies. In a healthy immune system, antibodies are created to fight infections. According to the National Institute of Health (NIH), it is estimated that over 24 million Americans are diagnosed with these disorders, and the cases are increasing (2005). These include systemic lupus, rheumatoid arthritis, and multiple sclerosis, to name a few. Autoimmune disorders have no cure and are chronic conditions that require lifelong treatment. This places a considerable burden on the healthcare system. A significant risk factor that has been linked to the formation of these diseases is the gut microbiome. The gut microbiome of the adult plays a vital role in the efficacy of the immune system. This ecosystem of various bacteria in the gastrointestinal system contribute to the formation and response of the human immune system (Zhang et al., 2015). This study aims to determine if a diverse microbiome can prevent autoimmune pathogenesis or decrease the severity of these disorders in patients. The case of systemic lupus erythematosus (SLE) is discussed as a prime example of an autoimmune disorder throughout this study.

Statement of the Problem

The human gut microbiome contributes not only to the health of the human immune system but also possibly to the pathogenesis of disease processes (Whu, 2012). Dysbiosis is the imbalance of this microbiome. It is understood that this dysbiosis contributes to bowel-related diseases, but what role does this play in other disease processes? Individually, regarding autoimmune disorders, how does the imbalance of the gut microbiome contribute to the

development of the immune system attacking itself and leading to an autoimmune disease? With the continued rising cases of autoimmune disorders, the role of the gut microbiome's influence on the human immune system must be understood.

Research Question

In adults, does the gut microbiome alter the risk for development or worsening of autoimmune disorders?

Methods

An extensive review of the current literature was completed. Databases searched included PubMed, DynaMed, Cochrane Library, Embase, and Clinical Key. The review of current meta-analysis, systematic reviews, cross-sectional, longitudinal, and survey methodologies will be analyzed. The search time frame was limited to the previous fifteen years. Keywords used and mesh terms included human microbiome, healthy microbiome, systemic lupus erythematous microbiome, immune function, dysbiosis, leaky gut, and autoimmune disorder microbiome. Inclusion criteria included peer-reviewed journals, meta-analysis, systematic reviews, randomized controlled trials, and case studies. Exclusion criteria originally included animal studies, pediatric, or geriatric focused research. The beforementioned exclusion criteria of animal studies limited the results as many initial studies are completed on animal test subjects before confirmation of data in human subjects. With the addition of studies that included germ-free animal subjects, the final research resulted in fourteen studies that were assessed furthermore for bias, quality of data, and relevance to the topic.

Literature Review

Previously the gastrointestinal tract was thought to be just an organ for digestion. With the advancing technology and increased research, the gut microbiome is hypothesized to play an important role in the immune system. Specifics of the role of this microbiome is still misunderstood. There have been common findings in autoimmune patients regarding a lack of or overabundance of certain bacteria in the gut. The consensus through the scientific community appears to be the unknown of which occurred first. Has dysbiosis caused autoimmune disorders, or is dysbiosis in the gut an occurrence that coincides with the autoimmune disorder due to the change in the immune system?

Defining the Gut Microbiome

An article by Cresci and Bawden (2015) provides a current understanding of how the gut microbiome develops from in utero through adulthood. Highlighted are the current research studies aimed at understanding how changes in the gut can influence the host's overall health. Learning the changes that can negatively alter the microbiome in all life stages could allow for targeted treatment. Topics addressed with the review include the influence of in utero changes, delivery method, infant feeding variances, changes with age, geographical effects, food supplies, stress alterations, pharmaceutical use, and gastric acid suppression. According to Cresci and Bawden (2015) "The gut microbiome is now becoming known for its role in metabolism, immune defense, and behavior" (para. 1).

Brody (2020) describes the microbiome as numerous microorganisms, over a trillion to be exact. All of these microorganisms, virus, bacteria, yeast, and other forms of life make up the entire microbiome inside and on each living individual. To better understand these numerous

life forms, many researchers are focusing on the gut microbiome. It is hypothesized that there are healthy balances and unhealthy balances regarding this microbiota. The key is to understand how the changes in the microbiota influence the health of the host.

The Human Microbiome Project (HMB) was initiated by the National Institutes of Health (NIH) in 2007. This project is focused on studying and cataloging the microbiota from five areas of the human body. These areas consist of the skin, mouth, nose, vagina, and colon. Data from 242 healthy adults was retrieved from a total of 15-18 sites per adult. All adults used in the HMB were carefully screened with physical examinations. These exams resulted in exclusion from the study if oral health was substandard, cutaneous lesions were present or the body mass index was higher than 24.5. The use of a metagenomic sequence and 16S ribosomal RNA gene cataloging were implemented for consistency. Over 800 strains have been discovered from this data set alone. This data is essential to this topic as the HMB establishes the diversity that has yet to be discovered in the human microbiome.

The data was processed using various sites, which could contribute to a limitation of the study. This allows for numerous lab and human errors. The HMB is a large-scale collaborative effort among many scientists. The HMB is the basis for all current research efforts regarding the gut microbiome.

Researchers are attempting to catalog the gut microbiome in a healthy individual. The microbiota in each person varies greatly. Commonalties among healthy subjects is being established. Data from the HMB study is being used currently for these efforts. This may lead to a better guideline for defining how the human microbiome can influence health or illnesses of the host.

As Arumugam et. al (2011) describes:

> A comparative metagenomic analysis of the human gut microbiomes of 39 individuals from 6 countries shows that despite this diversity, the microbiota composition can be classified into at least 3 distinct groups, or enterotypes. The enterotypes contain functional markers that correlate with individual features such as age and body mass index, a feature that may be of use in the diagnosis of numerous human disorders such as colorectal cancer and diabetes (pg. 180).

The Gut Microbiome and Relation to the Immune System

The review article by Shi, Li, Duan, and Niu (2017) provides an understanding of the gut microbiome and its relationship to the immune system. The gut microbiome is responsible for influencing not only the homeostasis of the gastrointestinal tract, but also the mucosal immune system (MIS) as well. This immune system consists of a lamina propria, epithelial cells, and lymph nodes. Together this anatomy of the MIS forms a barrier of protection for the host. When dysbiosis occurs, there is an imbalance between the healthy bacterial growth and the pathogenic bacteria. This dysbiosis triggers a mounted response from the MIS. Chronic inflammation can occur from the mounted immune response that the MIS is responsible for.

The inflammatory process and common markers seen are emphasized in this piece Shi, Li, Duan, and Niu (2017). One such marker discussed is found in obese subjects. In a healthy adult there are 4 groups of bacteria consisting of firmicutes, bacteroidetes, proteobacteria, and actinobacteria. In the obese subjects the ratio of firmicutes and bacteroidetes is decreased when compared to the ratio found in an adult of normal weight range. Another similarity was noted in the systemic lupus erythematous (SLE) patients researched as well, a decreased ratio of

firmicutes and bacteroidetes. The researchers concluded that a gut microbiome dysbiosis may lead to inflammatory process triggered by the MIS.

The authors used 92 resources for the review article. Both have listed no competing interests. While many resources from medical journals and research studies were implemented with the input of only two authors, bias could contribute to this review article. Another limitation of the review is that no information is given for the readers to be informed of the methods used to obtain the resources listed.

Round and Mazmanian (2009) discuss a review of findings that address the varying aspects of the bacterial colonies of the gut and their influence on the human immune system. Immune dysfunction is known to lead to many diseases, including autoimmune disorders. By highlighting the symbiotic relationship of the gut microbiome and the immune system, a theory is presented that the immune system thought to regulate microorganisms may be in fact regulated by the microorganisms. The gastrointestinal tract is the primary site of communication between the mucosal immune system and the host immune system. Proper immune function and improper immune function with gut dysbiosis are presented in this review.

The homeostasis of the gastrointestinal tract in germ free mice is the focus of the research presented by Round and Mazamanian (2009). A balance between pro and anti-inflammatory regulators is necessary for homeostasis. In the germ-free mice it was discovered a decreased amount of these regulators, also known as interleukins, was found. This could lead to the development of irritable bowel disease (IBD). The results will need to be confirmed in human subjects.

A significant limitation of this review includes that the inclusion and exclusion criteria were not presented. Therefore, some data presented may come from unreliable sources. The article is peer reviewed, but some bias may be present with only two authors contributing to the piece. The review did acknowledge gaps and that more research is in fact needed in the area of the influence of the gut microbiome on the human immune system since the focus was on germ-free mice.

The Gut Microbiome and Autoimmune Diseases

Clemente, Manasson, and Scher (2018) present a state-of-the-art review summarizing current knowledge regarding therapeutic changes to the gut microbiome and the resulting effect on the host's health and disease status. Available data is discussed regarding the state of gut microbiome dysbiosis and the possible contribution to autoimmune disorders. Human samples and animal models were sampled to correlate data trends in autoimmune diseases including, inflammatory bowel disorder (IBD), systemic lupus erythematosus (SLE), inflammatory arthritis, and multiple sclerosis. Randomized dietary intervention studies that assessed the manipulation of the diet to treat autoimmune disorders were also reviewed. These concluded insufficient evidence to show a correlation to warrant using diet modulation as a treatment for autoimmune disorders. This review encourages readers to continue to ask questions regarding the correlation between manipulation of the gut microbiome as a possible treatment option for patients with autoimmune disorders.

Clemente et al. (2018) searched PubMed using primarily American authors. Search inclusion consisted of cross-sectional, placebo studies, randomized control-trials, observational, prospective, meta-analyses, and population-based studies. Over 201 resources were used with a broad range of dates. While the amount of resources includes a large amount of data, the date

range could contribute to the limitations by the inclusion of outdated information. There were no date restrictions within the exclusion criteria. Case reports and case studies were excluded in their entirety from the database search. Also, the reference section of selected articles was reviewed to increase the data sources. This could also lead to a slight bias. The contributing authors cited no conflicting interest.

A cross-disease meta-analysis was presented by Duvallet, Gibbons, Gurry, Irizarry and Alm (2017) which included the data sets of 28 published case-control gut microbiome studies. The data from the 28 studies were termed the MicrobiomeHD post compilation. This study was the first to compare the gut microbiome across various disease processes versus one to two diseases in all other previous studies. The analysis of the microbiome data consisted of collecting, re-processing, and re-analyzing the study samples. Studies that only included data from children five years and younger were excluded from the meta-analysis. The authors analyzed data sets of ten disease processes. The goal was to pinpoint patterns across all researched diseases. The diseases included obesity, human immunodeficiency virus (HIV), irritable bowel disease (IBD), clostridium difficile infection (CDI), non-clostridium difficile infection (NCDI), autism spectrum disorder (ASD), crohn's disease (CD), liver cirrhosis (LC), ulcerative colitis (UC) and rheumatoid arthritis (RA). By comparing multiple studies for the individual disease processes, consistent shifts in the gut microbiome for each disease were identified.

The generalized outcome of this research was that there are no specific microbiota shifts for each disease. Thus, reaffirming that more research in this field is needed. Commonalities were found across many diseases, such as IBD patients are seen with a depleted gut microbiome while diarrheal disease states were seen with an increase in the gut microbiome flora. There are

various reasons for these shifts among different disease processes. Each host may have variations that affect the gut microbiome, community changes, and technical batch effects, to name a few. The study recommends that the science community begin to use a standardized form of analyzing the gut microbiome to increase the chances of discovering a common microbe that may be linked a specific disease process.

Author E. Alm did report a competing interest due to being a board member of OpenBiome, a stool bank that develops microbiome research-based treatments. This is a limitation of the article as E.A. could be biased for possible financial gain. All other authors reported no competing financial interests. The study aimed to eliminate inconsistencies with individual studies. Also addressed was that comparing data can be complicated due to the lack of one processing method. This strengthened the meta-analysis by eliminating these differences and re-analyzing in one consistent manner from various sources. The re-analysis data of MicrobiomeHD were consistent with the study sets original results. By reproducing the original study data sets, this also added strength to the study. This provided trends for the disease process regardless of the various data sets originally using varied research methods.

Lombardi et al. (2018) define the gut-brain-axis in their review:

> The gut-brain-axis refers to the bidirectional communication between the enteric nervous system and the central nervous system. Mounting evidence supports the premise that the intestinal microbiota plays a pivotal role in its function and has led to the more common and perhaps more accurate term gut-microbiota-brain axis (p.1)

This review provides readers with an understanding that many links have been found between dysbiosis of the gut and neurogenic diseases. While causation cannot be confirmed,

whether the disease or the dysbiosis occurred first, this article aims to present how the diet can affect the microbiota. These changes made via diet interventions may also change the responses of the mucosal and systemic immune systems. Of interest to this research is the focus on the gut microbe changes seen in patients with multiple sclerosis (MS). The dietary effects on the gut microbiome and the possible influence on MS is pertinent to this research.

Limitations of this author's manuscript include the use of resources with a large date span. Some of the data may be outdated as the original date of the 272 resources implemented originating in 1981. Various studies referenced in this article also used germ-free mice with no replication of found data in human sources. This is also a limitation of the data presented and must be kept in mind. The authors did declare that there are no conflicts of interest with this piece.

Multiple sclerosis (MS) is a disabling autoimmune disorder in which the host immune system attacks the myelin sheath of the nerve fibers. The pathogenesis of this disorder is still not fully understood. There has been an increased incidence of MS across the world but strikingly so in Japan. Animal subject studies have previously shown a common gut dysbiosis when infected with autoimmune encephalomyelitis (EAE). This finding led to Miyake et al. (2015) completing a controlled study to investigate if the human host with MS displayed a similar gut dysbiosis.

The gut microbiota of twenty patients with remitting-relapsing (RR) MS (MS20; aged 36.0 ± 7.2 years, 6 men and 14 women) was compared with the gut microbiota of forty healthy individuals (HC40; aged 27.2 ± 9.2 years, 23 men and 27 women) (Miyake et al., 2015). Also, both groups were compared with another eighteen healthy subjects (HC18; aged 21.9 ± 3.1 years) (Miyake et al., 2015). All subjects in the HC18 group gave fecal samples for months,

totaling 158 longitudinal samples. Implementing a high-throughput culture-independent pyrosequencing method analysis of the bacterial 16S ribosomal RNA (rRNA) was completed.

A moderate dysbiosis was found in the MS group. In total, twenty-one micro bacteria were found to be of significant difference in the gut microbiome between the MS20 and HC20 groups. Miyake et al. (2015) wrote, "both unweighted and weighted analyses showed a significant difference ($P < 0.05$) in the overall gut microbiota structure between HC40 and MS20 subjects" (p.13) When comparing the MS and HC18 samples, a variance consisting of clostridia clusters and bacteroidetes was discovered. A further phylogenic tree analysis of the clostridia were shown to be reduced in the MS gut microbiota. This species did not overlap with other clostridia species that are known for colonic T cell regulation. Colonic T cells prevent autoimmune reactions and allergies. It is hypothesized that this specific difference may be unique to MS patients. The author encourages readers to continue research aimed at correcting this specific dysbiosis as a potential treatment and possible prevention of MS.

Exclusion criteria for subjects studied included patients with primary or secondary progressive MS and any additional disease processes. All subjects also only provided fecal samples while in a remission state. Also, no subjects were prescribed antibiotics during the controlled trial so as not to alter the gut microbiome. Limitations of the study do include the sample size. The subjects were from one geographical area, which could also have some influence on the gut microbiome. To form a solid consensus in the alterations of the clostridia species of MS patients further research with a more extensive subject base and various geographical locations must be completed.

The exact cause of autoimmune disorders is still unknown. Many scientists and researchers have been attempting to answer this specific question. It is known that various

factors may contribute to the pathogenesis of autoimmune disorders. This includes a genetic predisposition, drugs, stress, geographical location, environmental exposures, and viral infections that trigger the immune system to attack itself. Among the most recent theories is the hypothesis that gut microbiota may trigger and worsen the formation of autoimmune disorders.

Xu et al. (2019) completed an extensive research review comparing data from over 112 resources to pinpoint causation between the gut microbiome and autoimmune diseases. While causation was not confirmed in the review of data, some possible links were presented. The inclusion studies focused on rheumatoid arthritis (RA), systemic lupus erythematous (SLE), spondylarthritis, irritable bowel diseases (IBD) and subsets of these disorders. In these diseases, the functionality of the aryl hydrocarbon receptor (AhR) ligand in the gut microbiome is established as a possible cause of the initiation or worsening of the autoimmune disorders. The authors did acknowledge that further work is needed regarding this ligand as a possible avenue for future treatment and prevention. Other possible treatments that influence gut microbiota also included fecal transplants, prebiotics, probiotics, and diet intervention. The authors declare that there is no conflict of interest.

Limitations of this review article include the methods for data inclusion and exclusion are not disclosed. Thus, verifying the original data for quality is difficult. The validity of the review article may be a misrepresentation of the original author's research data.

The Gut Microbiome and Systemic Lupus Erythematosus

Systemic lupus erythematous (SLE) is an autoimmune condition in which the body mounts an immune attack on the host (Mu et. al, 2017). Subsequent systemic inflammatory response effect all organs. SLE is a complex disease process treated with immunomodulators that decrease the body's immune response to slow the progression of organ damage. This study

highlights how manipulating the gut microbiota of animal models, germ free mice, regulated immune mediated inflammatory responses.

The use of symbiotic bacteria, five various lactobacillus strains, were used to increase the gut microbiota of mice presenting with nephritis as a secondary complication of SLE. Each week for five weeks, the mice in a controlled, sterile lab were evaluated for improvement. The mice provided additional lactobacilli dosing showed improved renal function and had an increased lifespan versus the control group. The researchers hypothesized this treatment contributed to an anti-inflammatory response in the gut mucosa of the mice. Mu et. al (2017) wrote "New knowledge of disease modulators, such as symbiotic bacteria, can enable fine-tuning of parts of the immune system, rather than suppressing it altogether" (para. 1).

Mu et al. (2017) declare that they have no competing interests. This study's glaring limitation includes that the data must be replicated in human subjects to confirm the findings. Future studies will have to be able to replicate the same outcomes in the human population.

Systemic erythematous lupus (SLE) is described as a complex disease process with limited treatment options. The mainstay treatments include immune suppression therapy, steroids, and symptomatic treatments. These all can have adverse side effects that lead to other complications compounding the already complex SLE. Yacoub et al. (2018) state the discovery of a more effective, targeted treatment option is urgent. SLE predominantly affects females and those of African American decent. This research focused on studies that analyzed primarily females and subjects of African American and Asian descent.

"Studies investigating the microbiota in the fecal matter of lupus patients, a significantly higher abundance of *Bacteroidetes* was found compared to the healthy controls. Compared to

healthy individuals, lupus patients have a *Firmicutes/Bacteroidetes* ratio that is almost 2.5 times smaller, indicating a strong correlation between dysbiosis and lupus" (Yacoub et al., 2018).

Another commonality found was that SLE flares in previously stable patients seem to correlate with recent administration of antibiotic therapy. Could this be due to the removal of the healthy gut bacteria, thus an overgrowth of the unhealthy bacteria? Yacoub et al. (2018) are unable to conclude if changes in the microbiota are causes of SLE or if a combination of factors influence the pathogenesis of this autoimmune disorder. It is highlighted that further dietary interventional studies are needed to focus on outcomes with the use of prebiotics, probiotics, and controlled diets to confirm if changes in the gut microbiota can influence the health status of SLE patients.

The articles and studies referenced in this review from Yacoub et al. (2017) included 72 resources. The authors of this review article are all affiliated with the Department of Medicine, University at Buffalo, NY. This could lead to bias of inclusion or exclusion criteria dependent upon the goal of the authors. Their methods of the research are not disclosed for review either.

The cross-sectional study completed by Azzouz et al. (2019), "matched blood and fecal samples from 61 female patients with SLE were obtained. Fecal 16 S rRNA analyses were performed, and sera profiled for antibacterial and autoantibody responses, with findings validated in two independent lupus cohorts" (pg. 947). All subjects included in the research study met the criteria for diagnosing of SLE based on criteria from the American College of Rheumatology. Inclusion criteria allowed for patients over 18 years of age, non-pregnant or breastfeeding, focus on females, confounding medical diseases, malignancy other than SLE skin complications, Cyclophosphamide in previous year, if using Methotrexate a stable dose over previous month, infections with or without hospitalization over previous 90 days and IgA

deficiency present. Ribosomal 16rNA gene sequencing was implemented for the analysis of all fecal samples.

The Azzouz et al. (2019) study linked a health status decline in SLE patients with paralleled declines in the overall diversity of the gut microbiome. Increased numbers of *Ruminococcus gnavus* (*RG*) were also found in with the diagnosis of nephritis. Subsequent fecal samples were also obtained in this cohort which resulted in increased numbers of sIgA coated *RG* bacteria.

Azzouz et al. (2019) concluded the following:

> "At the species level, patients with SLE displayed a mean 5-fold overabundance of an anaerobic Gram-positive taxon in the Firmicutes phylum and *Lachnospiraceae* family, identified as *Ruminococcus gnavus (RG*) (range 0.00%–10.79%, mean±SD 1.35%±2.01%) compared with controls (0.00%–1.27%, 0.25%±0.39%, Mann-Whitney, p=0.01). Strikingly, *RG* relative abundance correlated with lupus disease activity, as even patients with SLE with low disease activity had a mean 4-fold *RG* overrepresentation, while those with high disease activity had >8 fold greater *RG* abundance (Mann-Whitney, p=0.01)" (pg. 947).

This study shows an identification of increases in *RG* bacteria among SLE patients and may lead to a new avenue of focused treatment. *RG* bacteria could be implemented as a biomarker for SLE severity as well. Azzouz et al. (2019) acknowledge the limitation of this study is the failure of the research to prove if the increased *RG* bacteria contributed to the SLE patient health decline or if the *RG* bacteria increased due to the inflammation from the SLE process.

Discussion

Round and Mazmanian (2009) were able to discover lower numbers of interleukin-17 (IL-17), T helper 17 (TH17) cells and defective regulatory T (TReg) cells in germ free mice. This led to a decreased immune response in the germ-free mice. It was concluded that the intestinal microbiome may in fact influence the immune response, specifically the pro-inflammatory modulators and the anti-inflammatory modulators. In order to confirm that this occurs in the human body, human studies would be necessary. Raising germ-free humans is impossible. So, it was concluded that it is still uncertain if the shift in the microbiome leads to autoimmune disorders such as irritable bowel disease (IBD).

Almost similarly Shi, Li, Duan, and Niu (2017) state in their research that changes in the microbial community of the GI tract can influence the immunity of the host. If the microbiota of the GI tract is in homeostasis the immune system can actively combat inflammation. Shi et. al (2017) states "Dysbiosis of the gut microbiome is caused by the imbalance between the commensal and pathogenic microbiomes" (para. 1). Even with this specific statement, there was still a lack of a definitive conclusion and it was acknowledged that further research is needed to confirm these findings.

A cross disease meta-analysis of 28 case studies from Duvallet et. al (2017) confirmed that there is no specific dysbiosis for autoimmune diseases. The aim of this work was to compare and find a correlation between numerous auto-immune diseases. This has never been attempted prior as in the past only one to two disease states were compared. This work compared 10 disease states. The result was again inconclusive. With some diseases it was found that there was overabundance of bacteria while in others there was a lack of bacteria in the gut microbiome. Over 50% of the bacteria found in the 28 case studies responded to more than one

disease state. Duvallet et. al (2017) concluded that due to this overlap in various diseases the gut microbe changes may be a direct result of the diseases, not a cause. This confirmed once again that further work needs to be completed in order to detect a commonality for targeted treatment.

Conclusion

Autoimmune disorders cause the body's immune system to mistakenly attack itself. The outcome for the effected individual can range greatly. While some are left with mild symptoms others have serious outcomes, including death. The understanding of how the microbiome can be influenced to prevent and/or treat these conditions is of great importance.

Given the wide variances among each individual gut microbiome, the conclusion is with this research why it is such an undertaking for the scientific community. Regarding the data reviewed there is no specific healthy versus unhealthy pattern of the gut microbiome that can be applied to all individuals. The research also confirms more differences than similarities among humans. There are a wide variety of microbiome combinations found in a healthy individual. Many variances may cause interference with the stability of the microbiota population. These can include one's geography, diet, medications, and stress levels just to name a few. All factors have been a part of the reason as to why there is still no consensus regarding if, or how the gut microbiome can influence one's immune system. Even with all the data from numerous studies, there is no one defined healthy gut microbiome that can be applied to humans.

There is an enormous amount of evidence being contributed to this effort daily. In this data some trends are seemingly being found, but again no specifics can be pin-pointed due to the variances among individuals. Ongoing efforts will continue to attempt and categorize these

various microbiotas in hopes to determine their influence. When this is accomplished it is expected that may aid in treatment efforts for those suffering with autoimmune diseases.

Applicability to Clinical Practice

Autoimmune diseases are chronic conditions that place a heavy burden on the health care system. Further research is necessary to establish if the gut dysbiosis or the autoimmune disorder occurs first. As a provider, the benefits of knowledge in the influence of the gut microbiome regarding patients with autoimmune disorders will lead to increased human health and well-being.

With the information provided in the literature review, a sound understanding of the functionality of the gut microbiome may allow providers to prevent or treat dysbiosis. Once the clinical provider can restore the gut microbiome to a healthy state, the patient may experience better outcomes.

Unfortunately for providers, even with the research boom over the past decade or so into this area, these complex connections have yet to be deciphered. While we are aware that the gut microbiome is influential, it's role in health is still very misunderstood.

References

Arumugam, M., Raes, J., Pelletier, E., Paslier, D., Yamada, T., Mende, D., . . . Bork, P. (2011). Enterotypes of the human gut microbiome. *Nature*, 473, 174–180. https://dx.Doi.org/10.1038/nature09944

Azzouz, D., Omarbekova, A., Heguy, A., Schwudke, D., Gisch, N., Rovin, B., . . . Silverman, G. (2019). Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Annals of the Rheumatic Diseases*, 78, 947-956.

Brody, H. (2020). The Gut Microbiome. *Nature*, 577, 5. http://dx.doi.org/10.1038/d41586-020-00194-2

Clemente, J., Manasson, J., & Scher, J. (2018). The role of the gut microbiome in systemic inflammatory disease. *BMJ*, 360, 5145. http://dx.doi.org/10.1136/bmj.j5145

Cresci, G., & Bawden, E. (2015). Gut microbiome: What we do and don't know. *Nutrition in Clinical Practice*, 30(6), 734-746. http://dx.doi.org/10.1177/0884533615609899

Duvallet, C., Gibbons, S., Gurry, T., Irizarry, R., & Alm, E. (2017). Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. *Nature Communications*, 8(1), 1784. http://dx.doi.org/10.1038/s41467-017-01973-8

Lombardi, V., De Meirleir, K., Subramanian, K., Nourani, S., Dadga, R., Delaney, S., . . . Palotas, A. (2018). Nutritional modulation of the intestinal microbiota; Future opportunities for the prevention and treatment of neuroimmune and neuroinflammatory disease. *The Journal of Nutritional Biochemistry*, 61,1-16. http://dx.doi.org/10.1016/j.jnutbio.2018.04.004

Miyake, S., Kim, S., Suda, W., Oshima, K., Nakamura, M., Matsuoka, T., …Yamamura, T. (2015). Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia XIVa and IV clusters. *PLoS One*, 10, 9. http://dx.doi.org/10.1371/journal.pone.0137429

Mu, Q., Zhang, H., Liao, X., Lin, K., Liu, H., Edwards, M., … Luo, X. (2017). Control of lupus nephritis by changes of gut microbiota. *Microbiome*, 5(1), 73. http://dx.doi.org/10.1186/s40168-017-0300-8.

National Institutes of Health (NIH). (2012). A framework for human microbiome research. *Nature*, 486(7402), 215-221. http://dx.doi.org/10.1038/nature11209

NIH Autoimmune Diseases Coordinating Committee: Autoimmune Diseases Research Plan. (2005). Retrieved from https://www.niaid.nih.gov/sites/default/files/adccfinal.pdf

Round, J., & Mazmanian, S. (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*, 9(5), 313-323. http://dx.doi.org/10.1038/nri2515

Shi, N., Li, N., Duan, X., & Niu, H. (2017). Interaction between the gut microbiome and mucosal immune system. *Military Medical Research*, 4,14. http://dx.doi.org/10.1186/s40779-017-0122-9

Wu, H., & Wu, E. (2012). The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes*, 3(1), 4-14. http://dx.doi.org/10.4161/gmic.19320

Xu, H., Liu, M., Cao. J, Li, X., Fan, D., Xia, Y., … Zhao, H. (2019). The dynamic interplay between the gut microbiota and autoimmune diseases. *Journal of Immunology Research*, 7546047, 1-14. http://dx.doi.org/10.1155/2019/7546047

Yacoub, R., Jacob, A., Wlaschin, J., McGregor, M., Quigg, R., & Alexander, J. (2018). Lupus: The microbiome angle. *Immunobiology*, 223(6-7), 460-465. http://dx.doi.org/10.1016/j.imbio.2017.11.004

Zhang, Y., Li, S., Gan, R., Zhou, T., Xu, D., & Li, H. (2015) Impacts of gut bacteria on human health and diseases. *Int J Mol Sci*, 16, 7493-7519. http://dx.doi.org/10.3390/ijms16047493