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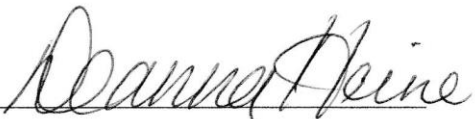Independent Study NURS 997

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PERMISSION

Title   Diet Manipulation and the Impact on the Gut Microbiome in Rheumatoid Arthritis

Department   Nursing

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Abstract

The American College of Rheumatology (2017) describes Rheumatoid Arthritis (RA) as the most common autoimmune arthritis. It affects 1% of the population (Khanna, Kumar, & Bhawna, 2017). RA is a progressive joint destruction disease causing increased difficulties with activities of daily living, pain, and deformities. Over the last ten years there has been progress in the treatment of RA. However, the disease continues to be devastating even with the best treatments to slow the progression of the disease. Recent research has focused on the gut microbiome and its impact on autoimmune disorders like RA. The human microbiome is composed of bacteria, archaea, viruses, and eukaryotic microbes. These microbes have tremendous potential to impact the physiology in both health and in disease (Shreiner, Kao, & Young, 2015). A dysfunction in this microbiome can cause gut dysbiosis, thus inducing inflammatory cascades and triggering RA (Sandhya, Danda, Sharma, & Scaria, 2015). Recent studies show diet manipulation can improve the gut microbiome, which then improves overall well-being (Singh et al., 2017). The aim of this review is to identify whether people with RA could experience symptom improvement by cultivating gut symbiosis with diet manipulation.

Keywords: Rheumatoid Arthritis, autoimmune disease, gut microbiome, gut dysbiosis, diet

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This case study is based on the examination of a fifty-nine-year-old Caucasian male who was seen in clinic for symptoms of malaise, muscle pain, and a fever of 102-103 degrees Fahrenheit. He had complained of these symptoms ongoing for five days. He was ultimately diagnosed with Influenza A, which was further complicated by immunosuppression related to his Rheumatoid Arthritis (RA) treatment.

RA is an autoimmune disease resulting in chronic inflammation of joints and in severe cases organ inflammation. RA occurs when T and B cells attack synovial proteins leading to inflammation of joints (Taneja, 2014). Long term inflammation to the joints can cause bone erosion and joint deformity. Not to mention extreme amounts of joint pain affecting multiple joints including the hands, wrists, elbows, knees, and ankles. There is no cure for the disease and it will inevitably progress without appropriate treatment ("The American College of Rheumatology", n.d.).

While infections and other environmental factors (e.g. smoking) have been studied extensively and have shown some association, a direct link between all the factors has been difficult to prove (Taneja, 2014). Over the last twenty years, development of new medications which include disease modifying anti-rheumatic drugs (DMARDs) and biologics, have offered an effective way to delay the progression of RA. While these medications have improved patients' quality of life, they do not come without risk and side effects. Disease modifying anti-rheumatic drugs (DMARDs) have offered success in disease suppression and symptom improvement by decreasing inflammation and preserving joints. Unfortunately, with immunosuppression the risk for opportunistic infections and disease increases. Immunosuppression places the patient at an increased risk for viral illness i.e. influenza, which

can also increase the risk for progression to a concomitant illness like pneumonia. This raises the

question: are DMARDs and biologics the only option for improving or slowing the progression

of RA? This also raises further questions about how diet can impact and improve the

microbiome, which may lead to a decrease in the inflammatory process of RA. In order to

appreciate the effects of the diet, one needs better understand the gut microbiome in RA. Recent

technological advancements and expanded efforts have led to a tremendous growth in the

collective knowledge of the human microbiome (Shreiner et al., 2015). This review will

highlight some of the important recent findings in this area of research. The cause and effect of

genetics on the gut microbiome, and the environmental influence on RA, have been thoroughly

studied over the last 20 years. Much research has found links between inflammatory diseases,

specific genes, and the human microbiota. The hypothesis is that chronic inflammation decreases

the permeability of the gut causing "leaky gut" syndrome. Alteration in the gastrointestinal

microbial environment is proven to be diet dependent (Singh et al., 2017). **Case Study:** S.F. is a

59 y/o Caucasian male with a past medical history of Rheumatoid Arthritis (RA) and

hypertension. He presented to clinic with symptoms of fatigue, chills, headache, cough, and

joint pain. These symptoms started five days prior to the visit. He reported that the joint pain

was not the typical RA joint pain he has felt in the past. The discomfort was described as more

of a "muscle weakness" that had gotten progressively worse. He denied any current or recent RA

flares. He denied rhinorrhea, sore throat, purulent drainage or sputum. He did endorse decreased

energy, appetite, and difficulty sleeping due to his cough. The cough was non-productive and

started with malaise five days prior to the clinic visit. He stated he had been taking over the

counter ibuprofen 400mg every four hours with slight symptom improvement.   However, his

fever re-occurred within three to four hours of treatment. He denied environmental allergies or

smoking. His work was as a customer service representative and was in contact with customers

on a regular basis. He reported that he lived with his wife and she had not been ill. He had not

received his influenza vaccine and had not had a pneumococcal vaccine either. His medication

list consisted of Lisinopril 10mg daily, Humira 40mg infusions every two weeks, methotrexate

10mg weekly, and an over the counter multivitamin.

S.F.'s physical findings showed vital signs of blood pressure 142/45, pulse 90, respiratory

rate 30 and temperature of 102.4 Fahrenheit. He had injected conjunctiva bilaterally and his ears

were negative for erythema or otitis media with effusion. He had no rhinorrhea. His lung sounds

were clear to auscultation and he exhibited no increased work of breathing with retraction, even

with an increased respiratory rate. His cardiac exam showed regular rate and rhythm without

murmurs or gallops.

The diagnosis differential was Influenza, atypical pneumonia, bronchitis, or an upper

respiratory infection. An influenza swab was performed in clinic and found to be positive for

influenza A. This patient was given Tamiflu 75mg every twelve hours for five days and

consulted on taking ibuprofen 400mg every four hours as need for a febrile state. The decision

to give Tamiflu beyond the forty-eight hours of symptom onset was due to his

immunosuppressed state. In this state, if the symptoms continued for a long period of time, he

had a higher propensity to develop concurrent illnesses like pneumonia. He was instructed to

return to clinic in two to three days if symptoms did not improve due to increased risk of viral

and/or bacterial pneumonia. If he had returned with ongoing or worsening symptoms, a chest x-

ray would have been reasonable to consider. He was also counseled on the importance of

adequate nutrition, rest, fluid intake, and to stay away from others until symptoms subsided. S.F.

was counseled on the importance of returning to the clinic, once he was symptom free, for the influenza vaccine and pneumococcal vaccine due to his immunosuppression.

Literature Review

For this literature review, an exhaustive search via CINAHL and Pub med was done with key terms "microbiome and Rheumatoid Arthritis" and "diet and Rheumatoid Arthritis". Due to the extensive amounts of research surrounding this subject the search was narrowed to twenty-one articles written from 2014 to 2018. After review of the literature, fourteen articles were found relevant to the scope of this paper and consisted of recent surveys, controlled cohorts, meta-analysis, systematic reviews, and animal studies. The patient case study described above involved an immunosuppressed individual with an acute illness. The following literature review seeks to understand the gut microbiome and the possibility of improving immunity and RA symptoms with diet manipulation.

Gut Microbiome

Genes found in the Major Histocompatibility Complex (MHC) along with some HLA-class II alleles have been shown to have associations in the predisposition for RA (Taneja, 2014). It was proposed that depending on one's genetic make-up, any type of gut dysbiosis could incite inflammatory or autoimmune diseases like RA (Sandhya et al., 2015). Singh et al. (2017) conflicted with Sandhya et al. (2015) by postulating that genotypes produce the human microbiome, thus predisposing one to RA. Hence, leaving us with questions of cause and effects.

In the past 10 years, many researchers have found links between gut dysbiosis and RA progression. It was hypothesized that the bacteria combination in the gut microbiome plays an important role in the pathogenesis of RA. However, this research is not conclusive and requires further study on the specific bacteria involved in the microbiome. The need for answers have

driven researchers to engage in shotgun metagenomics; resulting in the sequencing of the whole

bacterial genome (Singh et al., 2017). Both studies done by Marietta et al. (2016) and Chen et al.

(2016) proved that the homeostasis of gut microbiome bacteria tends to modulate the immune

function. An upset in that homeostasis induces inflammation. Marietta et al. (2016), showed this

by instilling abnormal bacteria into the gastrointestinal system of germ free mice; subsequently

resulting in increased inflammatory markers.

        Increased and chronic gut inflammation causes changes to the gastrointestinal epithelium

essentially resulting in a "leaky gut". Gut dysbiosis produces a pro-inflammatory environment

which compromises the intestinal integrity, consequently leaking gut bacteria in the systemic

immune system (Taneja, 2014). Therefore, permitting irregular microbiota to leach out

systemically. In doing so, the adaptive immune response is triggered, causing T cells and B cells

to attack healthy tissue or as in RA, the synovial tissues specifically (Taneja, 2014). Diet and

dental hygiene have been shown to affect the bacteria make up in the gut microbiome. Taneja

(2014) found a link between inflammation and triggering bacteria like Escherichia coli,

Mycoplasma fermentans, Klebsiella pneumonia and Porphyromonas gingivalis. Diet helps to

maintain the homeostatic gut environment by allowing the normal flora to thrive. This then

decreases the chances of a "leaky gut", subsequently decreasing RA flares.

        Interestingly, Chen et al. (2016) found that patients taking DMARDs like methotrexate

and hydroxychloroquine, showed a restored normal microbiota; implying another link between

microbiome and inflammatory processes. This could lead to the presumption that the case study

patient who was using DMARDs therapy, would most likely have homeostatic gut microbiome

therefore improving his immune state. Would urging patients to use a diet to boost homeostasis

prove to be beneficial in RA even with DMARDs?

Diet manipulation

As indicated earlier, homeostatic gut bacteria maintain the immune system by preventing

harmful bacteria, therefore decreasing "leaky gut" syndrome (Sandhya et al., 2015). The

literature suggested the diet re-engineers the microbiome to harbor and control therapeutic

bacteria. Many small studies have researched diet manipulation and the influence on RA

symptoms. Sundstrom, Johansson, and Rantapaa-Dahlqvist (2015) found no significant

correlation between diet and the development of RA.   However, other studies found that diet

affects the progression and symptom aggravation in RA, evidenced by decreasing the Disease

Activity Score (DAS-28) (Khanna, Jaiswal, & Gupta, 2017; Comella, Matilla, & Cuesta, 2015;

Tedeschi et al., 2017). The results showed that diet manipulation did not prevent RA but

decreased progression of joint destruction and pain symptoms.

The Mediterranean diet and the supervised fasting diet showed to improve gut bacteria,

important in improving cardiovascular health, Diabetes Mellitus, obesity, and inflammation

(Singh et al., 2017). These diets were found to be the most successful diets in improving

morning stiffness, number of swollen joints and decreasing the DAS-28 score (Comella et al.,

2015; Khanna et al., 2017). In most of the studies, the progression of RA is measured by the

DAS-28 survey, C-reactive protein (CRP), and Estimated sedimentation rate (ESR). Disease

Activity Score-28 (DAS-28) is a questionnaire that subjectively screens pain in 28 different

joints ("National Rheumatoid Arthritis Society", n.d.). The Mediterranean diet incorporates

increased amounts of oleic acid, omega-3 fatty acids, unrefined carbohydrates, and

phytochemicals.

Diets high in omega-3 polyunsaturated fats have shown a higher rate in disease remission

and decreased use of DMARDs in RA (Comella et al., 2016). Polyunsaturated fats play a pivotal

role in gut homeostasis (Navarini, Antonella, Gabriele, & Magiotta, 2017). Thereby, helping to

maintain adequate gut bacteria, which enables optimal nutrient absorption and decreasing pro-

inflammatory properties. Forsyth et al. (2017) found the Mediterranean diet to improve pain and

function in RA. This is compelling evidence for conjunctive use of diet with medication therapy

and symptom management. Conversely, there is insufficient evidence to support using

Mediterranean diet in the prevention of RA (Khanna et al., 2017).

The supervised fasting diet is another diet recommendation that reduces inflammation

and helps to improve the symptoms of RA. It comprises of 200-300 kcal per day for seven to ten

days and then is followed by a vegan diet for one year. Similar to the Mediterranean diet the

fasting portion of the diet includes ingesting specific phytochemicals. The intake of vegetable

broth, herbal teas, parsley, garlic, potatoes, juice extracts from carrots, beets, and celery

decreases CD4+ lymphocyte activation which has been identified as a negative factor in the

progression of RA (Khanna et al., 2017). The vegan diet eliminates animal protein subsequently

decreasing inflammatory bacteria like bacteroides, allistipes, bilophilia, and ruminococcus

(Singh et al., 2017). A study on impact of diet in inflammatory bowel disease, revealed

increased lactobacilli and bifidofacterium, after ingesting pea protein intake over animal protein

(Singh et al., 2017). Lactobacilli and bifidofacterium were identified as important bacteria in gut

homeostasis. This has helped to identify the types beneficial gut bacteria that preserves the

epithelium of the gut.

The common Western diet is known to be high in sugar and saturated fats. This has been

shown to increase inflammation by way of decreasing lactobacilli (Singh et al., 2017). A study

by Tedeschi et al. (2017) found that foods and beverages with sugar worsened RA symptoms.

Consequently, the traditional western diet negatively impacts RA by increasing inflammation.

Other diets like Paleo, *The Gut Makeover*, and prebiotics/probiotics were not thoroughly studied

or had too small of study groups to be recognized as being effective in disease modulation for

RA (Lawrence, & Hyde, 2017; Sandhya et al., 2015).

Relevance to case

It is obvious there is need for continued DMARDs therapy in RA in order to decrease

devastating progression of joint destruction. However, continuing to understand the physiology

of the microbiome and manipulation of the diet is an important aspect in the management

equation. S.F., in the case study, would be best served to continue on Humira (adalimumab) and

Methotrexate; as long as his RA disease continues to be suppressed and he continues have no

significant side effects of the medication. According to research, sustaining a specific diet that

supports gut health is needed to maintain an optimal immune system. In doing so, S.F.'s RA

symptoms could be decreased as well as decreasing the chances in obtaining concurrent illnesses.

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Conclusion

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In conclusion, the literature review suggested that diets modulate gut microbiome. In

doing so, it prevents gut permeability and decreases the potential cause for bacteria to leach

systemically. Studies have shown that the gut microbiome has an important role in disease

pathology and management. There is a need for further understanding of gut microbes and their

relevance in the pathology of autoimmune disorders. Studies of microbiome are complex and

extensive due to the need to follow-up with complex individuals with RA (Sandhya et al. 2015).

Also, individual gut microbiome cannot be used for diagnostic criteria for RA, as there is not

enough research on the complete role in RA pathology. The microbiome is important and should

be acknowledged for further study in Geno mapping in order to develop diagnostic criteria and

further disease management of RA. Diet manipulation by using Mediterranean diet or

Supervised fasting diet improves DAS-28 scores exhibiting decreased RA joint pain and functional improvement. More extensive studies would be beneficial in understanding bacteria pathophysiology and dietary manipulation in hopes to predict potential disease and RA prevention. This may help lead to development of optimal dietary regimens that would lead to gut symbiosis.

Learning points

- The human microbiome plays an important role in autoimmune disorders.

- Understanding gut microbiome, will help to develop conjunctive management and modulation of inflammatory disease.

- Diet manipulation can help maintain disease advancement by creating gut symbiosis.

- Evidence has shown that following the Mediterranean diet and the supervised fasting diet will improve RA symptoms.

- In RA, diet should be used in conjunction with medical therapy such as DMARDs.

- Diet should not be used as a preventative therapy for RA but can be used in the management of symptoms.

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