Autoimmune Diseases and Diet: A Literature Review

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June 19, 2011

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A senior research project submitted in partial requirement for the degree
Doctor of Chiropractic

Abstract

OBJECTIVE – This article provides a compellation of literature to show the multiple theories to the causes of autoimmune disease and their relationship to diet. Emphasis will be placed on the physiological effects of poor diet on the immune system, intestinal permeability, mucosal barrier function, and inflammation. Finally three main autoimmune diseases related to diet will be discussed.

METHODS – A computer search of PubMed, Ebscohost, and Dynaweb databases at Logan College of Chiropractic. The search came up with over 105,826 articles on autoimmune, but only 1144 for autoimmune and diet. Roughly 350 were directly related to Celiac disease. References from many texts and publications have been used as well.

CONCLUSION – While there are many theories and causes of autoimmunity, this author is concentrating on the similarities between the most accepted modern theories and their similarities to food allergies. Certain autoimmune diseases such as celiac and inflammatory bowel disease have been found to have major contributing factors that are related to certain foods. Evidence has shown that there is a startling correlation between immune dysfunction and the resulting autoimmune disease.

Keywords: autoimmune, intestinal permeability, mucosal barrier,

Introduction

Autoimmune diseases affect between 5 and 8 percent of the population, making them the third most common category of disease after cancer and heart disease**.** The National Institutes of Health claims that there have been more than 80 different types of autoimmune disorders diagnosed[2]. There are also 15 known diseases that are a direct result of an autoimmune response, and links of more than 80 other conditions to autoimmunity[14]. Dr. Vasquez stated in his book that autoimmunity is a direct reflection of immune dysfunction.[3]

In a healthy normal human, the immune system's white blood cells (WBC's) work to protect the body from harmful substances, called antigens. Antigens can include viruses, bacteria, or toxins. The immune system normally produces antibodies that destroy these harmful substances. In patients with an autoimmune disorder, the immune system can't tell the difference between healthy body tissue and antigens. This will result in an immune response that causes the WBC's to attack normal body tissues. This responses hypersensitivity reaction is very similar to the immune response in allergies[2].

Dorland's 31st Medical Dictionary defines autoimmune disease as**,** a disorder caused by an immune response directed against self antigens[4]. Meriman-Webster Medical Dictionary defines autoimmune disease as, of, relating to, or caused by antibodies or T cells that attack molecules, cells, or tissues of the organism producing them[1]. However, some diseases, such as systemic lupus erythematosus and rheumatoid arthritis are often classified as autoimmune diseases even though their pathogenesis is unclear[4].

There is evidence to support that autoimmune diseases share common threads by genetics, diet, and a combination of both[25]. Much of the current research has shown that the treatments and theories of the autoimmune diseases related to diet, which include celiac and inflammatory bowel disease, are starting to change. If an autoimmune reaction would theoretically be similar to an allergic response, what would happen if you looked at the relationship of all different food allergies, food sensitivity, and food intolerance, and their impact on the immune system?

Discussion

Theories

The concept that the body attacks itself has baffled physicians for centuries and because of that there have been many theories about how and why autoimmune diseases happen. The three most accepted theories of the autoimmune process that remain are molecular mimicry, the by standard effect, and the most recent one which is the hygiene theory. The first one is called molecular mimicry, where microbial antigens that are formed closely resemble self-antigens[15]. The microbial antigens stimulate an immune response in the body, but not only are the microbial antigens targeted; the self-antigens are targeted as well. As part of this theory, once the molecular mimicry process has started it is self perpetuating and irreversible[13]. The difference in this theory from the other two is molecular mimicry is not a beginning stage of autoimmunity; it will only help exacerbate an existing autoimmune response[15], it will never start one. Recent

evidence has shown that molecular mimicry is strongly involved in the formation of reactive arthritis and anklyosing spondlyitis[38, 39].

The second theory that is most accepted is referred to as the bystander effect. This theory is based on when the immune system attacks the bad microorganisms in the body. As a consequence there is a direct damage to the surrounding tissues as accidental casualties otherwise known as "friendly fire"[37]. This has only been found to happen when the new antigen, that is being attack by the immune system, is presented as an orally administered trigger antigen[16]. There is still some confusion and questioning to whether the pathogens in the body mimic self-antigens, release sequestered self-antigens, or both[15]. Recently, there has been research that has come out in the last decade to show that the bystander effect is more for the development certain autoimmune conditions, such as drug-induced lupus[35]. This theory has also been suggested to contribute to heavy metal-induced autoimmunity[36].

The third most recent theory that is also becoming the most accepted is called the hygiene theory. This theory argues that countries with higher burdens of helminthes and other parasitic organisms have less prevalence of autoimmune diseases[24]. Research has shown that a down regulation of Th2 immune response leading to an increased Th1 immune response, which is due to an absence of helminthes and other bacterial infection, is characteristic of autoimmune and inflammatory diseases[17, 18]. It has been shown in different research that the Th2 immune response is related more to celiac disease and the Th1 response is more involved with inflammatory bowel disease. Over the past few years it has been shown that the immune system adaptation and the imbalance between the Th1 and Th2 immune responses are key elements in the autoimmune process and many other pathological conditions[19, 23].

Intestinal Permeability

There are many researchers and doctors that believe the single most important factor with regard to autoimmune disease and diet is intestinal permeability. The permeability of the intestinal barrier is controlled by the tight junctions. These junctions were originally thought of as a concrete and non regulating barrier[26]. This thought process has changed over the past decade with research showing that tight junctions are a complex meshwork of proteins which need to have a complex form of interaction between each cell in order to be effective[15]. In the past few years the discovery has been made of the single most important molecules that have been found to be the main modulator of tight junction permeability is zonulin. Not only does this molecule show how the intestinal barrier is regulated in the presence of health and disease, but recent research has shown that zonulin is the only modulator of intercellular tight junctions and is involved in the passage of macromolecules and, therefore, in delicate balance of the immune response[20,21]. There has recently been a change in the classical theories in the development of autoimmune diseases. The change suggests that there are certain autoimmune processes that can be halted if the interplay between genes and environmental triggers is prevented or changed. The most beneficial and successful results have been shown by reestablishing the zonulin intestinal barrier function[21].

Intestinal Defense

The main system to prevent antigens from reaching the systemic circulation is the Gut-Associated Lymphoid Tissue (GALT)[43]. The GALT is composed of immune inductive sites and

immune effector sites. Dysfunction of the gut mucosa can cause impairment of mucosal barrier function and development of localized or systemic inflammatory and autoimmune processes[33]. So how does this happen? Well for starters a build up for microbial colonization of several different organisms secrete protein digesting enzymes that actually "digest" the defense immunoglobulins that we have in our intestinal mucosa. The enzymes produced by Candida can lyse not only immunoglobulins but keratin and collagen cells too[40]. For this process to even occur there has to be a massive shift in the colonization of certain bacteria. This occurs when there is a problem with carbohydrate digestion[3]. This problem is what causes the shift of the microbes. Over time this will result in inflammation which only causes further problems with carbohydrate digestion and an even greater shift in bacterial colonization[41]. The final breakdown of this defense occurs when the mucosal enzymes are lost and malabsorption, maldigestion, and absorption of other problematic molecules, as seen in patients with inflammatory bowel disease[42]. Once this occurs, the gates of protection have been broken.

Inflammation

Inflammation is a term that has been used a lot in research recently. Inflammation is a response by the body when the immune system is activated to counter a threat. A healthy immune system is vital to good health, but ongoing immune activation and inflammation can lead to many different problems throughout the body[34]. The body is always adapting to the stressors that are placed on it and the best first line of defense humans have is inflammation.

The process of inflammation is a local reactive change that involves the release of antibacterial agents from nearby cells that defend the host against infection. Inflammation works by containing the infection or injurious agent and also serves as a defense mechanism for the body so it can restore itself to normal physiological form and function. This protective response is designed to help the body get rid of the initial cause of cell injury and the consequences of that injury. Cell injury can be a result of many different factors; the main ones are foreign bodies, trauma, immune reactions and infections, and physical or chemical agents.

The inflammatory response consists of two reactions, a vascular and a cellular reaction. These reactions are mediated by chemical factors derived from plasma proteins or cells. The classic signs of inflammation include fever, leukocytosis, and the presence of certain acute-phase proteins. This inflammation process is one of our main lines of defense and repair, but the body is not designed to deal with inflammation for long periods of time. A recent study showed that long-standing intestinal inflammation is associated with colorectal cancer, small-bowel adenocarcinomas, lymphomas, and autoimmune diseases[32]. After the inflammation process has begun, the binding of antigens with immunoglobulins forms immune complexes that can deposit in parenchymal and synovial tissues where a localized immune response causes inflammation and organ dysfucntion[3]. Later in the paper the discussion about the consumption of food over time triggers allergens to increase, which will also increase inflammation leading to intestinal permeability[8] and in turn greater absorption of intestinal contents.

Inflammation from Diet

One of the most over looked ways that Americans get acute or chronic inflammation is through the foods that are eaten in the American diet. Well how are Americans as a whole eating? Although we as Americans can choose from a wide variety of foods, some diets are just plain nutrient deficient. The more distance the average intakes of the American diet fall below the RDA's, the greater the likelihood that some people will have inadequate nutrient supplementation. According to the United States Department of Agriculture of the 10 leading causes of death in the United States, 4 of them —including the top 3—are associated with diets that are too high in calories, fat, saturated fat, cholesterol, and sodium, or too low in fiber-containing foods[63].

Dr. Alex Vasquez talks about the significant difference between food allergies and adverse food reactions and explains how medical literature underestimates the high prevalence of food allergies because of inconsistent terminology, imperfect laboratory assesments[5], and assuming that healthy people are only allergic/sensitive to one or two foods. This has been shown to be inaccurate and patients with food allergies/sensitivities, they must avoid several (3-10) commonly eaten foods to obtain clinical response and improvement[3, 6, 7]. How important are adverse food reactions? Research has proven that adverse food reactions are more than just a tummy ache. They can exacerbate many different illnesses; here are a few rhinitis[44], thyroid disease[45], recurrent otitis media[46], hyperactivity disorders[47], gastrointestinal inflammation[48], hypertension[49], depression[50], epilepsy[51], migraines[52] ,and joint pain[53].

It has been discovered that the common symptoms of food allergies are very similar to a regular allergic response. The common symptoms of an allergic response are skin rash,

abdominal pain, angioedema, and bronchoconstriction[3]. Every medical field teaches its students how to identify an allergic response, but in the past decade there has been a growing concern from many doctors that think there might be a delayed onset or "hidden" food allergies in their patients that are preventing them from improving symptomatically. These "hidden" food allergies are clinically significant in the sense that they are causing the patient unknown problems, and are much more difficult to diagnose[3].

In his book, Dr. Vasquez breaks down the difference in terminology between food sensitivity and food intolerance. He defines food sensitivity is an immune response to adverse food reactions that is not mediated by anti-bodies. An example of this would be food induced irritable bowel syndrome[54]. The definition of food intolerance is an adverse food reaction associated with poor nutrition status and/or impaired hepatic detoxification that is not immune-mediated. The classic example of this category would be MSG sensitivity. Obviously there is going to be a certain amount of overlap between food allergies, food sensitivity, and food intolerance in some people all depending on their current state of physiology, inflammation, diet, and genetics.

Breakdown of Intestinal Permeability

As described above the tight junctions and main molecule zonulin are what keep the gut closed off from the outside world. After the inflammation in the gut starts to break down the zonulin and tight junctions, intestinal permeability becomes faulty. Another term that has been used for this process has been labeled leaky gut. The intestinal wall should function as a tightly regulated

barrier that accomplishes two tasks: absorption of nutrients, and exclusion of antigens, foreign debris, microbes and microbial antigens, and indigestible food residues. If this protection is compromised there is an increase in the amount of yeast, bacteria, and foods that can get through the intestinal barrier. This will result in difficulty in nutrient absorption, waste removal, and systemic inflammation[3, 9]. It has been documented clinically that when this process happens many patients will experience no gastrointestinal symptoms at all. A small number of patients may have minimal signs and symptoms including diarrhea, constipation, abdominal pain, fatigue, general food intolerances[3]. What else can cause problems with the mucosal barrier? Studies have shown there can be several cytokines with immune and radicals cells that can cause dysfunction of the intestinal mucosal barrier. This happens during the active phase of inflammatory bowel disease[22].

Intestinal permeability can be damaged through the main protection area on that covers the villi of the intestine, that would be the called the mucosal lining. The research shows that this area will be damaged mainly through bacterial overgrowth or microbial colonization. This occurs when there is an imbalance of the "good bacteria" and the "bad bacteria". Bacteria has not only been found to stay in the body for years after the removal of the main infection[58,59] but, it has also been discovered that bacterial overgrowth is a common problem in the diabetic, elderly, and immunosuppressed[10]. As time goes on there is the high probability that the overgrowth of bacteria/microbes will lead to irritable bowel syndrome, as well as myalgias and systemic immune activateion[11]. Just how common is bacterial overgrowth? Two astounding studies published in 2004 revealed that the occurrence of bacterial overgrowth of the small intestines is seen in 84% of patients with irritable bowel syndrome[10] and 100% of patients with fibromyalgia[12]. Also it has been noted that the activation of immunity cells by foods or its

components from gut microbes could participate in the impairment of intestinal mucosa and the development of intestinal and/or systemic inflammation[58].

Once the mucosal lining has been damaged there is a high demand put on the immune system to protect the body from the foreign invaders. Once the foreign bacteria, yeast, and/or food break through the lining into the blood stream the body has to defend them off. Since the immune system is the most metabolically expensive system to run in the body, and matter has limitations, the body can only fight for so long until it starts to exhaust itself.

Celiac Disease

When you think about autoimmune conditions relating to diet, there are two main diseases that come to mind, celiac disease and inflammatory bowel disease. Celiac disease is the poster board for autoimmune conditions related to diet, but how prevalent is it? Celiac has been a growing problem more and more in society over the past few years and affects all ages. With proper monitoring of gluten intake and providing nutritional supplementation[59], the people diagnosed can lead relatively normal lives without complication. There has been a growing awareness in society about celiac disease that can be easily seen in grocery stores, restaurants, and food manufacturers. One area that celiac has been found to be rising in is sports. Athletes that have celiac disease often have problems with iron absorption which can easily lead to anemia. They have also been found to have problems with vitamin D and calcium absorption which can potentially lead to poor bone growth, health and possibly osteoporosis. Even athletes with known and long-standing celiac disease can still compete at high levels. There is an additional

need for care and supervision in making sure there is no disruption in their gluten-free diet, which can lead to a flare-up of symptoms and very easily decrease their performance[61].

There are a number of complications that can occur with celiac disease, nutritional (growth failure in children, malnutrition, vitamin deficiencies), hematologic (anemia), neurological (peripheral neuropathy), and hepatic (cytolysis, cirrhosis) [60] to name a few. It has been found that a gluten-free diet will help to minimize the occurrence of most complications and over time correct the over-mortality related to these complications. The results of a gluten free diet on a patient with celiac can be noticed in few days to a few weeks. This is depended on the progression of the disease.

Inflammatory Bowel Disease

Inflammatory bowel diseases can be divided into two major disorders: Crohn's disease and ulcerative colitis. People diagnosed with inflammatory bowel disease are six times more likely to develop colorectal cancer than the general population and have a higher frequency of multiple episodes of colorectal cancers[62]. Ulcerative colitis has been found most commonly in the rectum and sigmoid colon, whereas Crohn's disease has been found to be more evenly distributed between the different colon segments. People diagnosed with inflammatory bowel disease often question their doctors about diet because of the lack of public understanding about the disease. These dietary suggestions have been derived from an accumulation of sources. They are as stated; nutritional deficiency screening, avoiding foods that worsen symptoms, eating smaller meals at more frequent intervals, drinking adequate fluids, avoiding caffeine and alcohol, taking vitamin/mineral supplementation, eliminating dairy if lactose intolerant, limiting excess fat,

reducing carbohydrates and reducing high-fiber foods during flares[63]. Recent data has shown that the incidence of inflammatory bowel disease is increasing. There are a few suggestions as to why this disease has risen so steeply in the last decade. One explanation is dietary factors such as the spread of the "Western" diet, high in fat and protein but low in fruits and vegetables. Another explanation is the lack of knowledge of the people suffering with the disease has also risen proportionally with the disease. Addressing the educational challenges is critical in caring for the people suffering from inflammatory bowel disease.

What are the treatment options for the different phases of inflammatory bowel disease? For the acute phase of the disease emergency medical treatment has been shown to help. Once the acute phase has passed though, the main focus is on finding the environmental factors that have been found to be triggers for inflammatory bowel disease in that person[64]. The single most important environmental factor in terms of the gut is diet. We are what we eat, you can't run an engine on poor fuel, yet we as humans pollute and toxify our systems to the brink of disease and still expect our bodies to run at full capacity. Proper nutrition and micronutrients assist the body by subtly strengthening its capacity for self-healing and regeneration. Education, confirmation, and a reflection into ones illness, create insight and a basis for coping.

Crohn's Disease

Crohns disease is defined as a chronic inflammatory condition of the gastrointestinal tract, characterized by trans-luminal inflammation, a discontinuous pattern of distribution, and fistulae. The symptoms of Crohn's vary but commonly include diarrhea, abdominal pain, weight loss, blood or mucus in the stool, perineal pain, discharge, and irritation resulting from perianal

fistulae. There could also be extra-intestinal manifestations of the disease that would include arthritis, uveitis, and skin rash[66].

Even though the etiology of Crohns disease remains unknown current theories suggest that the disease results from a genetic predisposition, regulatory defects in the gut mucosal immune system, and environmental triggers[66]. The environmental triggers that have been linked with Crohns disease include smoking, high sugar intake in the diet, and the delicate balance of the beneficial and harmful bacteria in the gut. There have been debates to whether certain bacteria cultured from the intestinal tissue of people that have diagnosed with Crohns disease were found to have been the cause of Crohns disease[66].

It has been shown that the majority of patients diagnosed with Crohn's disease eventually require surgical intervention. Unfortunately, recent statistics show that postsurgical success tends to be short lived. There are a significant number of patients that experience a clinical relapse and many require additional operations, there isn't any data to show if the additional operations were a success or not. There is no clinical or scientific explanation for why the pathogenesis of this postoperative recurrence happens. This phenomenon is poorly understood and, currently, there are no reliable tools to predict when and in whom these diseases will recur[65].

Ulcerative Colitis

The second type of inflammatory bowel disease is ulcerative colitis. Ulcerative colitis is defined as a complex disease in which genetic, environmental and microbial factors drive chronic intestinal inflammation that finally lead to extensive tissue damage[68]. The symptoms of

ulcerative colitis and Crohns differ slightly to the extent that ulcerative colitis has been known to have mucus like and bloody stools along with tenesmus. There have been population based studies with follow up over the last few decades that show the extent of the ulcerative colitis. Not only has this diagnosis increased, but the pathology has only varied slightly in that time frame[67]. This means that the disease isn't getting worse; it's just becoming more common in the American population.

Ulcerative colitis is very unpredictable. It can vary from a single attack to chronic symptoms that can have a juristic reduction on the quality of life. If this disease progresses it can very possibly lead to disease, colectomy or even to the development of colitis-associated colorectal cancer in some cases[68].

Recently there have been some minor breakthroughs with regard to the discovery of predictive clinical factors and biomarkers to help the discovery of the disease[67]. The goal in identifying these markers early is the hope that we may eventually develop a more personalized, tailored therapy to the individual.

Conclusion

Autoimmune diseases have been a mind puzzler for doctors for centuries. The understanding of the diseases has improved over the past few decades, but unfortunately the treatments haven't had much success[65]. There is a growing amount of research on celiac and inflammatory bowel diseases. A part of the research is directed toward the end stages of the diseases with a growing

portion on trying to identify the major causative factors of these diseases. The main factors that are being studied are environment, diet, and genetics.

There is strong evidence to support that diet has a direct impact on the inflammation process in the digestive tract[3, 9, 56]. The inflammation received from the American diet has been shown to be more prevalent[55] and have a greater impact on overall health then once thought. This has been found to be due to a high prevalence of food allergies because of inconsistent terminology, imperfect laboratory assessments, and assuming people are only allergic to one or two foods[3]. This has been disproven in people with food allergies that need to avoid anywhere from 3-10 commonly eaten foods to obtain a clinical response and improvement[3, 6, 7]. The inflammatory process whether chronic or acute has a direct impact on the intestinal permeability[3,9,10,11] and the intestinal defense portion of the digestive system[3,22,40,41,42]. If either of these two protection barriers is compromised then the body goes through an autoimmune reaction, which has been shown to be very similar to an allergic response[3].

More research is defiantly needed in the area of treatment options, especially for the treatment of chronic intestinal inflammation with diet modification. This author hopes that researchers will publish more work showing physiological and histological changes in the intestinal lumen before and after a modification of the patient's diet. Along with that this author hopes researchers will start to show more evidence of the correlation of autoimmune diseases and allergic reactions. Since an autoimmune disease has very similar characteristics as an allergic response in the body, treating the allergic response by getting rid of the allergen should essentially help deal with the physiologic symptoms of the autoimmune disease.

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