EVIDENCE FOR A POSSIBLE ROLE OF GLUTEN IN THE ETIOLOGY OF DIABETES MELLITUS

BY

ILIANNA PASCHALIDIS

A thesis submitted to the Graduate Faculty of

THE UNIVERSITY OF BRIDGEPORT

In partial fulfillment of the requirements

For the degree of

MASTER OF SCIENCE

In Human Nutrition

December 18, 2008

Bridgeport, Connecticut

Approved by:

_____

DR. BARRY KENDLER

TABLE OF CONTENTS

ABSTRACT:

Gluten is a wheat kernel protein made of gliadins and glutenins. It can be found in all forms of wheat, rye, oats, and barley. Celiac disease (CD) is a permanent autoimmune reaction to the consumption of gluten. There may be signs for CD, but many times it is asymptomatic. CD patients suffer from malabsorption issues, neurological problems, and a number of different diseases. CD is most often found among patients with Type 1 diabetes (T1D), in that these conditions are both genetically predisposed, contain the same HLA genotypes, can be environmentally triggered, and impact the same areas of the body. Jejunal biopsies have tested positive for severe inflammation with the onset of both diseases. Eliminating gluten has been shown to reverse intestinal damage. Elimination diets also improve insulin secretion, increase glycemic control, and help sick patients to put weight back on for body mass index recovery. The two diseases are being diagnosed together during early life. Not getting this diagnosis early only worsens the conditions and brings a much younger mortality rate. This worldwide epidemic seems to have strong geographical factors. Accordingly, there is a need to find the cause.

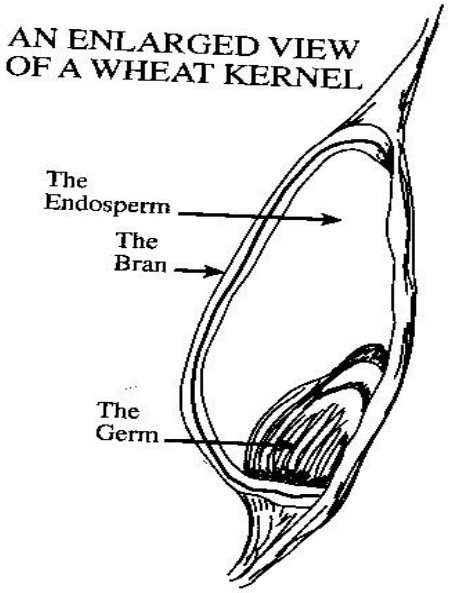
Together CD and T1D are rising epidemics, and it is possible that gluten is the predisposing factor for these two diseases.

INTRODUCTION:

Food allergens are proteins found in food, and once they are digested they travel through the bloodstream. The proteins travel to places in the body where allergy symptoms are known to occur: the lungs, skin, nose, throat, and our gastrointestinal tract. [1] The IgE antibodies will spot these proteins coming in, and as the body's defense it will release chemicals like histamines, thus allergy symptoms become present.[1] These days we have a much higher prevalence for food intolerance than for a mere food allergy alone. Food intolerances lead to autoimmune diseases such as CD and T1D.

COMPOSITION OF GLUTEN:

Gluten is a protein composed of gliadins and glutenins, which are found



inside the endosperm of the wheat kernel.[2] After the starch gets washed away the gluten is left behind. This protein is best described as a sticky, gummy, elastic substance, which is useful for thickening food, and helping it to rise. It is found in all the different forms of wheat including spelt, kamut, durum, semolina, oats, matza, etc. Gluten is also found in other grains such as: rye, tritical (a mixture of rye and wheat), and barley. [3, 4, and 5]

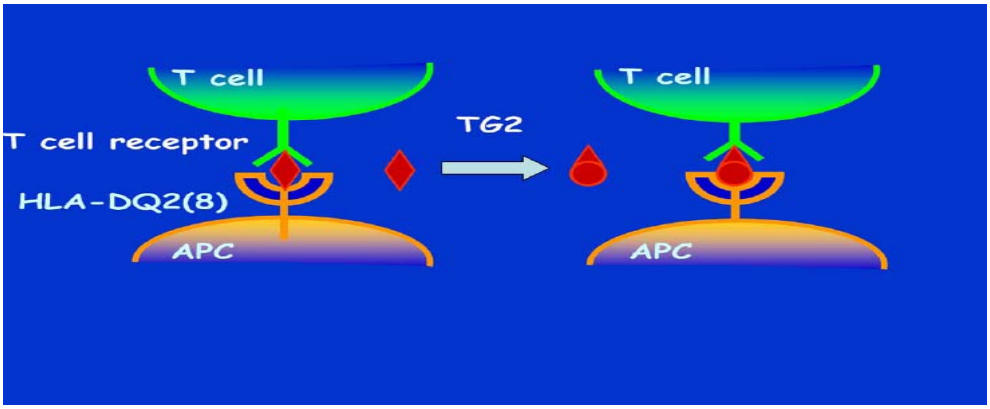
Gluten sensitivity manifests in people through two different forms: CD or a gluten intolerance. This is very different from the IgE antibody reacting to a food allergy. [5] Gluten intolerance is a heightened immune reaction to the gluten protein, which is linked to neurological problems like migraines, depression, anxiety, autism, MS, and ADHD. On the other hand, CD is a permanent autoimmune reaction. CD is known to cause damage to the villi of the small intestines and for causing classic gastrointestinal symptoms. Extreme damage to the villi of the small intestines and the inflammation cause a severe malabsorption problem. Nutrient malabsorption deficiencies include vitamins A, D, K, E, folic acid, B12, and iron. GI symptoms only account for ½ of CD patients. [7]. The autoimmune reaction causes a large number of other disorders such as osteopenic bone disease and osteoporosis, dental anomolies, reduced stature, infertility, lactose

intolerance, ataxia, iron deficiency anemia, central and peripheral effects on the nervous system, and internal hemorrhaging. It is also linked to many autoimmune disorders, examples would include nephritis, acidosis, lupus, thyroid disease, myasthenia gravis, rheumatoid arthritis, Addison's disease, and a possible link to the epidemic of T1D. [2, 3, 4, 6, and 7]. CD is diagnosed either through intestinal biopsies, serum antibody tests, or the disappearance of symptoms after gluten is removed from the patient's diet. [3]

Generally speaking, CD and certain gluten associated diseases (GAD's) are T-cell mediated diseases. [7] The most common genetic markers for the disease are human genotypes DQ2 and DQ8. Both the DQ2 and DQ8 are bound to the human leukocyte antigen (HLA), which is an antigen that prepares the cell's surface for essential elements in immune function and presents the protein to the body's T cells. HLA is also linked to other autoimmune disorders like T1D. [3, 6] It is known that the DQ2 gene is most common for the CD patient, and will typically be found in 90-95% of them. The DQ8 genotype is only present in 5-10% of the cases. [3, 8] Studies show that 20-50% of all humans carry this DQ2 gene and most likely many more that have not been discovered yet. [3]

Tissue transglutaminase (TG2) is an enterocyte enzyme that breaks down gluten, and also has a primary role in the development of disease. [3,

6] TG2 is the enzyme that helps to chemically bind the HLA to the DQ2 and DQ8 by changing gluten into negatively charged glutamic acid. [6] This leads to a greater gluten-binding affinity and more opportunities for T cell response against the gluten and associated CD. [6] The following receptor binding figure illustrates this relationship.



The same toll-like receptors (TLR) that are involved in our wound and tissue repair help to activate the TG2 in the small intestines. They alert the immune system to pathogens. [6] In a healthy individual with no signs of CD, the TG2 would remain inactive in the small intestines, and therefore inflammation would not develop. [6]

Diabetes is an inability for the body to properly use or secrete insulin from the pancreas. Insulin keeps serum glucose levels in control and also monitors glucose absorption into our cells. Insulin should be released from

the pancreas when eating as blood glucose levels are increased. [4, 8] Blood sugar levels are maintained at normal levels because the insulin promotes storage of the excess glucose. Two characteristics of T1D are hyperglycemic (having excess amounts of blood sugar levels) and the occurrence of glycosuria, meaning that the kidneys are sending out extra glucose through the body's urine. [4]

Autoimmune diabetes is insulin dependent. The body's T cells attack and kill its own insulin-producing islet of langerhans β cells. Sixty to eighty percent of the β cells are destroyed by the time symptoms occur. [4, 9]

Although this was diagnosed early in life, it is now also occurring in other age groups.

For example children with T1D have the highest amounts of autoantibodies in their systems. These help to easily identify a current disease. [9, 10] The three major autoantigens in T1D are those against tyrosine phosphatase (1A-2), glutamic acid decarboxylase (GAD-65), and insulin. [9]

A striking similarity in CD and T1D is that both disorders are strongly connected to HLA, especially with the genes DQ2 and DQ8, which are vulnerable to disease. [8, 9] Both CD and T1D have become epidemics, and both can be triggered by environmental factors. It is unclear whether or not food allergies can be the cause of T1D.

If the body identifies gluten as an allergen then an antibody to it might bind with the insulin receptors before the insulin ever gets a chance to slow down the insulin response. This speeds up the onset of T1D. [2] Antibodies affect a plethora of pancreatic β cells. Moreover, there are many other possible factors, both genetic and environment. The association between CD and T1D increases every day. The occurrence of CD and T1D happens in every 1 in 200 people treated for immune damage to the intestinal lining. [10] The latest studies for CD and T1D show a prevalence of 5.4 - 7.4% of CD in patients with AIDDM. [3]

The purpose of this paper is to see if gluten is responsible for the etiology of T1D.

LITERATURE REVIEW:

The fact that CD has a higher occurrence rate with T1D patients has been known for quite some time. [11] Their seems to be a direct relationship between the presence of gluten in the diet and the length of time of exposure. [11, 12] It is possible that if CD remains untreated, then the inflammation in the small intestines from the gluten, and internal virus infections, may cause AIDDM. [11]

It has already been shown among the BB rats and NOD mice that the presence of gluten and soy proteins changes the rate of development of

diabetes. [12]

The jejunum is the middle section of the small intestines, which connects the ileum and the duodenum. There is a suggestion that T1D may be derived from the intestines because of the inflammation that occurs there. [12]

A study was conducted by retrieving tissue samples from the small intestines of 17 T1D children. Their biopsies had no existing signs of CD and their diets contained no gluten restrictions. This study also included a control group of 50 subjects, all at the same age range. Neither group had any sign of anti-endomysial antibodies, or anti-transglutaminase antibodies. [12] The biopsies were cut into pieces, stored in different animal serums (such as rabbit), and observed through the immunohistochemistry technique. [12] They kept a close watch on T cell activation through staining techniques, and observed the immunofluorescent colors through the microscope of an analysis imaging system. [12]

Along with those two study groups there were tissue samples taken from another 12 T1D patients, and another 8 control participants for tissue culture studies. [12] These biopsies were studied invitro with gliadin or ovalbumin (albumin taken from egg whites) and studied for either cell lining inflammation or T cell activation. The samples were then prepped for cryosectioning and just as the previous group, went through the

immunohistochemcal analysis. [12]

The organ cultures showed a much higher inflammatory reaction in the biopsies that were exposed to gliadin, and there was an increase in the T cells for CD25 in the lamina propria lining. [12] Overall, the results showed that the T1D patients had significant inflammation in the jejunal mucosal samples. The immunohistochemistry showed greater amounts of HLA II and intracellular adhesion molecule 1, which leads to greater amounts of cytokines that create inflammation. [12] The lymphocytes also rapidly increased with the presence of the gliadin, causing the rectum to become inflamed for the patients with T1D. These reactions all mirrored the same outcomes present in biopsies for CD, and all the T1Ds had the HLA genes present. [12]

It seems that eliminating gluten from the diet of animals, such as mice, protects them from the onset of diabetes. [12, 13] However, this conclusion has yet to be proven in humans. A gluten-free diet does, however, reduce the prevalence of T1D in CD patients. [13]

A study designed to determine if gluten could be related to the islet autoimmunity included 7 children all under six years old.[13] The 7 youngsters were placed on a gluten elimination diet for a duration of 12 months, afterwards they would follow another 12 month diet that would re-

introduce the gluten. The 7 subjects chosen were all blood relatives to people who have T1D and all contained at least 2 auto antibodies for autoimmune diabetes. [13]

Before the study began, the children's parents all underwent a 48 hour lesson plan on how to successfully administer a gluten elimination diet. [13] All the patients underwent blood serum testing before starting their diets, and these tests were continued every 3 months. Oral glucose tolerance tests (OGTTs) were taken before the start, and then every 6 months. The last OGTT would be after the 24 month completion. Along with the serum testing, the insulin autoantibodies were tested quarterly, as well as at the start and finish. The gliadin antibodies were measured through the entire process. [13]

The study used a biochemical technique (ELISA) to measure the gliadin antibodies present. ELISA is an enzyme-linked immunosorbent assay, and a useful tool for spotting antibodies or antigens. [13] The insulin autoantibodies were measured with radio binding assay (RBA), which is thought to be much more useful for finding insulin autoantibodies than ELISA would be. [13, 14]

The results of the gliadin antibody tests were supportive of the fact that all the parents complied with the gluten elimination in their child's diet. There was no evidence of the presence of autoantibodies to tissue

transglutaminase in any of the children. [13]

It was surprising that after the gluten elimination portion of the study had been completed, there was no major difference within the islet auto antibody levels. The difference in the test readings had only shifted from measurement P=0.2 to P=0.4. [13]

Furthermore, any changes the youngsters went through individually did not reflect any significant difference between the times of having gluten present or absent in their diets. [13] Only one child had a significant decrease in the insulin autoantibodies during the wheat-free portion of the study. [13] The child was diagnosed with diabetes once the gluten was re-introduced into the diet. [13] The other six children experienced either an increase in diabetes antibodies or their levels all remained the same during the gluten elimination period. Once the gluten was introduced another one of the six youngsters was diagnosed with AIDDM. This gave a total of 2 out of 7 children being diagnosed with diabetes once the gluten was re-introduced. Those results were compared to a historical control group whose decreased numbers of antibodies during gluten elimination had a shared percentage for their ratios.

Their conclusions were that eliminating gluten from the diet had no effect on the quantity of diabetic auto antibodies in the subject's systems.

The islet autoimmunity never changed by changing the diet. This is much different than what would have occurred if the patient had CD antibodies. These studies show a decrease in the islet autoantibodies with a diet eliminating gluten. [13] Unfortunately, the cohort that was used did not have the same preliminary findings, such as already having auto antibodies present and being genetically a 1st degree relative for diabetes. The biggest difference of all was that the control group included subjects that already had CD. What the study shows is that dietary gluten is not a leading factor in islet auto formation of antibodies for patients who are genetically susceptible to diabetes. [13] This still leaves many questions yet unanswered. There is a window of time before diabetes onset occurs. Thus possible efforts can be made to reverse the clinical diagnosis. [15]

It is useful to look at what happens between gluten consumption and insulin production. Seventeen people in Italy were chosen to participate in this study. They were 1st degree relatives of patients who had T1D. This study was conducted as a follow up from the previous study discussed. [15] The same protocol was used to measure the antibodies from the patient's blood serum. Out of a perspective 601 candidates, the 17 chosen, as in the previous study, had at least two antibodies and were high risk candidates for developing diabetes. Six of the subjects chosen were male, and their mean age was 16 years old. [15]

Along with the same antibody protocol, they also used the same gluten elimination technique. Again the subjects participated in a 6 month diet with no gluten, and then another 6 months with the gluten re-introduced. Once again everyone was taught how to successfully execute a gluten-free diet protocol. The patients reported in throughout the study to confirm that they were sticking to their gluten free intake. [15]They also followed the same time line for autoantibody testing. Blood samples were taken before and after the study, and during the study they would be drawn and measured quarterly. [15] The intra venous glucose tolerance test (IVGTT) was taken 3 times, before the study began, after the first 6 months of gluten free diet, and after the final six months with gluten included in the diet. [15] Insulin resistance sensitivity was measured using a mathematical equation system known as HOMA, homeostasis model assessment - insulin resistance. [15] A Micro-particle Enzyme Immunoassay was used to measure the serum insulin. [15] The autoantibody readings were done by radio-binding, immunoprecipitation, and also immunofluorescence. [15] They were also able to do a comparison analysis every six months using the Wilcoxon Signed rank test. [15]

At the start, 17 of the subjects had the islet cell antibodies (ICA) and glutamic acid decarboxylase (GADA). Protein tyrosine islet antigen (IA-2A) was found to be in 12 patients. Insulin autoantibody (IAA) was in 8

subjects. There were seven patients that had all four antibodies. Six patients had two antibodies, and four patients had three. [15]

Unfortunately, during the first six months, two of the subjects did not follow through with the gluten elimination diet, so they were eliminated from the study. [15] All together three subjects developed diabetes. The 1st subject was diagnosed during the gluten free portion, the next person was diagnosed when the gluten was re-introduced. The third subject was diagnosed with diabetes after the 12 months of diet study had finished. [15] Overall, there were no significant changes to report in the autoantibody titers. [15] When the gluten elimination diet was over, 11 of 14 subjects showed an increased insulin response from their IVGTT. When the patients returned to a diet with gluten, 10 of 13 patients now came up with a sudden decrease in their insulin response. [15] Similarly, the homeostasis model assessment-insulin resistance (HOMA-IR) went down during gluten elimination in 9 of 14 patients, but then increased in 11 out of 13 patients when the gluten was returned to the diet. [15] There was a minor decrease for the fasting plasma insulin levels in the first six months, but a major increase occurred when gluten re-entered the diet. [15]

Once again, the results show that gluten does not impact the autoantibody titers. However, gluten had a direct effect on the secretion of insulin. Once the gluten was removed, the outcome for insulin was quite

positive. Accordingly, it is possible, that gluten can be part of the early development stages preceding diabetes. [15] The study also found a correlation between insulin secretion, and absorption, just as the results from HOMA - IR had shown. [15] There is speculation that the changes in insulin may have been from the different forms of carbohydrates being introduced to the diet, and not necessarily a reaction from removing gluten. It should definitely be noted that the subjects requested remaining on a gluten elimination diet longer, due to their feelings of health improvement. [15]

In 2002 the rate of CD in the general public was 0.01- 0.03%. [16] The rate for CD found in T1D children was 1-10%. [16] The numbers over the last six years have increased, but the fact is that people who have autoimmune diabetes have been shown for years to have higher rates of CD.

Eleven diabetic children were picked out of the John Radcliffe Hospital in Oxford. [16] Ten of the children carried the anti-endomysial antibodies (EMA), and one child carried anti-gliadin antibodies (AGA), this represented 4.8% of their clinic's patients. [16] All 11 subjects underwent an endoscopy test for their jejunal biopsies. The results showed all the positive physical markings for CD, and the children were immediately placed on gluten free diets (9GFD0). [16] Their AGA and EMA levels were tested every 3 months until the antibodies were gone, and to be safe, once every year thereafter.

The methods used to spot the EMAs and IgAs were biopsy techniques using immunofluorescence indirectly, and UV light immunofluorescence.

When CD was determined, each subject was matched with two control subjects that also had AIDDM. They were matched up according to their gender, age, and the length of time they had diabetes. The control subjects had no sign of CD, with a negative count for any AGA or EMAs. [16]

The children's C-peptide levels were checked once yearly, but every 3 months they had their weight, height, and hemoglobin A checked. Their insulin was monitored daily, and recorded at every clinic appointment. [16] The GFD was monitored for the 11 children for four years while they were being studied along with the control group.

The BMI's Standard Deviation score and hemoglobin A matched each subject to their two controls. This also included all the levels and measurements taken every three months. They used an Anova Model for all the information that was obtained, in order to show what kind of effect the CD was having on the subjects BMI, and hemoglobin A. [16]

The average age for the CD onset was 11 years, 2 months old. The outcomes show that the time it took for CD to develop after the subject had diabetes onset was 3.8 years. [16] The 11 children in the study had lower levels for their BMI SDS before they were diagnosed with Celiac Disease compared to the BMI SDS of the control group. The two groups, subjects

and controls, were both monitored with the same amounts of insulin every day. On their yearly check for C peptides, the levels had not changed for any of the subjects.

Six of the youngsters on the GFD allowed a repeat biopsy test of their small bowels, and it was found that their antibody levels dropped to zero in only 3 to 6 months time. [16] After one year of not eating gluten, the BMI SDS tests completely reversed between the controls and subjects, the latter now being the ones with the lower BMI as well as their HbA1 readings. The only thing remaining about the same for the two groups was their insulin levels and care. The adherence to a GFD treatment had a lowering effect on both the BMI and HbA1, and kept the children's glycemic numbers at healthy levels.

The fact that the BMI was lower in diabetics just before the onset of CD was possibly due to the damage done to the villi of the small intestines, and the malabsorption issues. [16] After following gluten elimination for 12 months, the healthy BMI levels made a full recovery, and healing in the small intestine's lining. [16] Once both study groups reached their pubescent years, they were retested, and, astonishingly, it was the control group that had higher HbA1. [16] The 11 children who remained on GFD all remained at their healthy glycemic levels, and did not experience a decline. How the type of carbohydrate consumed effects the insulin sensitivity is

unclear. This was a positive example of the importance that can come from the removal of gluten in a diabetics dietary intake. [16]

According to the 2006 study, the rate of CD in children with T1D across Europe has reached 2-8%, displaying an ever growing epidemic. [17] This next study involved 33 Danish children from a region that is known for having a high percentage of T1D in their children. It was a population based study in southern Denmark, and subjects were obtained from the pediatric departments of 4 different counties. [17] The youngsters for this study were all under the age of 16, and were selected according to weight, height, and antibody blood samples. The serum samples were measured for: IgG, IgA, AGA, and anti-edomysial antibodies (EMA), and anti-tissue transglutaminase antibodies (tTGA). [17] Once again, the study used immunofluorescence testing, along with enzyme-linked immunosorbent assay. [17] If blood work came back with a questionable amount for the subject's blood antigen levels, then they had to undergo an endoscopic intestinal biopsy. [17] A gluten elimination diet was administered to anyone who had damage to their small intestinal lining. [17] For a two year period the patients had quarterly follow up doctors visits, and all the blood work and measurements were repeated. After two years, the patients had the opportunity to have a follow up endoscope biopsy in order to assess any changes related to being gluten free. [17]

The statistical measurements were performed using Intercooled STATA 7, and once again Wilcoxon's Test using the P valve system. [17]

The children all had been living with diabetes for at least 3 years, but only five of the subjects had a CD onset and were following a gluten-free regime. Of the patients tested to participate in the study, their blood samples showed a very strong relationship with the co-existence of tTGAs with EMAs. [17] Any patients carrying CD showed a similarity in that their diagnoses of diabetes came much earlier in life. [17] The CD patients had reduced growth stature, and weight, and reported many more symptoms at their quarterly check-ins. [17]

Only two patients were not able to maintain the gluten free lifestyle, leaving 31 subjects. [17] Antibodies for 24 of the subjects were completely eliminated on a GFD within 3 months to 2 years. [17] The other seven patients did have a decline in antibody numbers, but they never experienced a complete disappearance. [17]

When the study had commenced, the subjects on the GFD showed an increased weight, along with an increased height for children under the age of 14. [17] They had an increase in hemoglobin, and an increase in their blood ferritin levels, and also their folate. [17] CD is known for malabsorption issues with iron and folic acid, which makes these outcomes clinically very significant. Unlike the previous study, these subjects had no

changes in their blood levels for HbA1. [16, 17]

Eighteen subjects returned for their intestinal biopsy, after consuming their diet with no gluten for 2 years. The intestinal linings for 14 of the patients had healed completely, and four subjects had partial healing. [17] Those children with partial healing only consumed a partial GFD. [17] Only two of the patients were recorded as having a decreased incidence of hypoglycemia. [17]

The following study was done in northwest Iran. It involved 100 subjects with T1Ds and a control group of 150 people with no sign of diabetes. Of those chosen as study subjects, there were 42 males and 58 females, all between 7 and 50 years old. [18] The control group contained 68 males and 82 females, who ranged from 4 to 50 years old. [18] Before the study started, all the people selected were tested for tTGA, along with IgA levels. [18]

It is noteworthy that the tTGA blood work results disclosed that the study group included 8 positive people, but the control group also tested positive for 3 people. [18] Like the last study the tTGA positive subjects had all been diagnosed at very early ages with diabetes, only there were not enough positive subjects this time to have sufficient statistical power in this study. [17, 18] All the tTGA positive females had villous atrophy in their small intestine biopsies. [18]

Eight percent of the diabetic subjects tested positive for CD, which is very typical of the ratios, to date, within the European population. [18] This study also gave further support to the fact that CD is more prevalent among younger age groups with diabetes. [18] There is also a hypothesis that large amounts of wheat in the diet, as in Iran and here in the U.S., helps to keep symptoms hidden. [18] The study did suggest that eliminating gluten would support a healthier life for the young diabetics, but further studies are needed to support that. [18] The ratios that were reported in the study showed that 8% of diabetics were positive for CD. [18] This is much higher than the mean average being 3.5%. [19] It is debated if CD testing methods need to be more accurate, with the disease under-diagnosed. They have reported an alarming 20.9% of CD prevalence in T1D for the children of Saudi Arabia, 21.3% in Libya, 16.3% in Algeria, 12.3% of the Danish, and, as previously
stated, 1-8% across the U.S. and Europe. [18] The lowest percentile reported in this study was 6.2% in the U.K. [18]

These percentages are alarming when considering secondary diseases and disorders associated with CD. Damage to the intestines and GI tract can also lead to cancer. [19]

This next study spanned the largest follow-up time thus far, from 1964 – 1994. [19] In this 30 year time frame, researchers were able to observe

over 10,000 Swedish CD patients, and determine the actual cause of the patients death. [19] The system of diagnosis for every patient was done using the 7th and 9th edition of the International Classification of Diseases. [19] Through all thirty years the people that were diagnosed as to having CD totaled 11,455 patients. [19] Exclusions were made according to whether they were immigrants, if they had died, or their information was lost. [19] The number of people used in this mortality study was 10,032 CD patients. [19] In order to keep an accurate statistical reading, they used standardized mortality ratios, known as SMRs. [19] This SMR would compare the number of subjects in the study to the numbers of mortalities that were expected. [19] The average amount of time patients had follow-up visits was just over eight years. More than 5,000 of the patients were first admitted to the hospital before they were even two years old. The mean age for the other half of the group that was hospitalized was just over 17 years. [19]

All together, this study observed 828 deaths. The SMR for patients with CD were two times greater than that of the normal death rate for the entire Swedish population. [19] The death rate ratios remained similar from year to year, whether the patient was male or female. [19]

Any patient that was hospitalized for the first time after turning two years old, was at a much greater risk for a earlier mortality rate. [19]

Among the patients that were taken to the hospital before turning two years old, there were 11 deaths, and two of them were due to endocrine disorders. [19] Diabetes was the leading factor for the combined total of endocrine-associated deaths; in fact it accounted for half the deaths in its category. [19] Furthermore, they found diabetes to be prevalent among all different patient cases. As long as the CD existed there was a good chance T1D could as well. [19]

The highest death totals came from the people who were not hospitalized until the age range of 10-40 years old. [19] The death rates were noticeably higher for people that had other diseases accompanying their CD diagnosis, but these patients were also accounted for being older in age, the mean year being 29. [19] This study further demonstrated how important it is for CD patients to find an early diagnosis. [19]

DISCUSSION:

The question as whether or not a patient with T1D should be tested for CD is definitely answered in the affirmative, based on the peer-reviewed biomedical literature. Screening for this statistical relationship should not be questioned at this point in time. CD occurs among patients with T1D around 30 times more than the average population. [20]

It is still unresolved whether or not gluten can be the actual cause of

autoimmune diabetes. There are a lot of correlations between these two diseases, along with genetic factors, and autoimmune reactions such as intestinal inflammation, and a conflict between receptors. It could be a combination of a great many things, with gluten just being one of these. For example, it could be gliadin acting with another enteral virus in the system.

Animal models showed diabetes to be dependent on both genetic background and the type of virus that may have damaged the β-cells. [9] It is possible for humans too, that genetic markers for family, virus, and nutritional protein must match for the onset of diabetes to take place.

If it were true that gluten is not a factor in the diabetes onset, then why is it that the relationship these two diseases share happens to be so geographically prevalent? How can we explain the decreased amount of these shared diseases among populations who traditionally rely on rice products for dietary intake? Their low gluten intake also mirrors the low numbers of patients who have CD and T1D.

Consistent with every study was the fact that the earlier the T1D patient was diagnosed with CD, the more favorable the prognosis. Early adherence to a gluten-free diet seemed to be helpful in all the cases documented.

My hope is that physicians will be more attuned to, and sensitive to, the possible existence of CD being present in their patients. There also

needs to be a greater awareness among the general population of the profound impact that food has on our biological systems.

It is quite beneficial for parents to keep gluten eliminated from their child's diet until they reach 12 months of age. This window of time is crucial for children developing autoimmune disorders, and food intolerances.

A major concern to me in these studies was their number of subjects. In the second study of the literature review, they tested whether or not gluten is the cause of islet autoimmunity. [13] This is an extremely important question that is now debated. The conclusion that they came up with was that gluten was not a predominant factor in T1D. However, the study only contained 7 subjects. Moreover, by the end of their study 2 of the 7 tested positive for T1D. How can 2 out of 7 people not be considered a significant ratio? A follow up study was conducted, but once again consisted of a limited number of subjects. It was promising to see that the patients requested remaining on the GFD, which is not a very easy life change to comply with. It shows that the patients experienced a profound difference in health once the gluten had been removed. Unfortunately this study lacked a control group. They did have a historical control group for comparison, but I really don't think a study should be run without one.

The hardest part, I believe, in all of the studies is the patient compliance. Gluten is so highly used all over the world for its baking

properties, and being economical gluten is added to many different products. This makes a gluten elimination diet more of a complete lifestyle change, and not an inexpensive one for the average consumer.

There are still a lot of questions that must be answered. It would be interesting to begin a new study starting an infant subject group on a GFD diet. The study would begin with the mother as soon as the child was conceived. The mom would also have to follow a strict GFD, so that there would be no cross contamination with any part of gluten for the developing fetus. The infant would have to be a first degree relative for inheriting T1D. In this way, we may be able to determine if total gluten elimination stops diabetes from occurring. If not, we might at least be able to see if the onset of diabetes could be delayed.

There are also questions about whether or not gluten may be having different autoimmune reactions, in the body, at different points in life. A lot of times people don't even begin to show any symptoms until later on in life, and at other times it may remain completely asymptomatic.

There is a great need for answers to these questions, and furthermore greater definitive studies are needed.

Conclusion:

Gluten is the protein found inside of the wheat kernel. It is made up of gliadins and glutenins. It is found in all different forms of wheat, rye, and barley. CD is a permanent autoimmune disorder that occurs as a result of gluten consumption. The most common symptoms are villous atrophy of the small intestines and gastrointestinal symptoms. Half the time the disease is asymptomatic. CD leads to extreme malabsorption issues, neurological damage, and many autoimmune disorders. CD and T1D seem to have an extremely close relationship to one another. They carry the same genetic factors and HLA (DQ2 & DQ8) genotypes. They are both thought to originate in the intestines. They can both be environmentally triggered, and they have both been increasing together at statistically high rates. CD is found among people with diabetes, more than with any other diagnosis worldwide.

Recently, it has been shown possible to reverse the destruction of the villous atrophy, simply by removing gluten from the diet. Even if gluten is not responsible for causing the onset of T1D, it could be speeding up the rate of diabetes development. Is gluten involved in the etiology of diabetes mellitus? It appears so, but the question is still unresolved at the present time….

References:

1) US Department of Health and Human Services. National Institute of Allergy and Infectious Disease. Food Allergy An Overview. NIH Publication No. 04-5518. July 2004.

2) Medical Nutrition From Marz, 2nd Edition. Marz Russell, ND, M.Ac.O.M. Natural College of Naturopathic Medicine. Omni Press. Oct1, 1999. Pgs. 362-365.

3) Helms S. Celiac Disease and gluten- associated diseases. Alternative Medicine Review 2005; 10(3): 172-192.

4) Prescription For Nutritional Healing, 4th Edition. Balch Phyllis, CNC. Penguin Group, Inc. New York. 2006. Pgs. 313-316.

5) Murray J. The widening spectrum of celiac disease. American Journal of Clinical Nutrition, Vol.69, No.3, 354-365, March 1999.

6) Koning F. A tertiary twist to the transglutaminase tale, PLoS Biology 5(12): e337.doi: 10, 1371.

7) Gheller A, Steven H, Abdulkarim A. Celiac Disease: Celiac Sprue, Gluten- Sensitive Enteropathy. Clinical Medicine & Research. 2(4). 71-72. 2004.

8) Knip M, Siljander H. Autoimmune mechanisms in type 1 diabetes. Autoimmunity Reviews. 2008 Jul; 7(7): 550-557.

9) Natkins A, Lernmark A. Autoimmune type 1 diabetes: resolved and unresolved issues. J. Clin. Invest. 108(9): 1247-1252 (2001).

10) Biros E, Jordan M, Baxter A. Genes Mediating Environment Interactions in Type 1 Diabetes. The Review of Diabetic Studies. 2(4): 192-207. 2005.

11) Frisk G, Hansson T, Dahlborn I, et al. A unifying hypothesis on the development of type 1 diabetes and celiac disease: Gluten consumption may be a shared causative factor. C.2007. El Sevier Ltd. Medical Hypothesis (2008) 70, 1207-1209.

12) Auricchio R, Paparo F, Maglio M, et al. Invitro- deranged intestinal immune response to gliadin in type 1 diabetes. (Immunology and

Transplantation). Diabetes 53.7(July 2004): p1680(4).

13) Hummel M, Bonifacio E, Naserke H, et al. Elimination of Dietary Gluten Does Not Reduce Titers of Type 1 Diabetes- Associated Autoantibodies in High- Risk Subjects. Diabetes Care 26(7). 25: 1111-1116, July 2002.

14) Marchal C, Bridel M, Goffaux F, et al. Superiority of radio binding assay over ELISA for detection of IAAs in newly diagnosed type 1 diabetic children. Diabetes Care, 14(1) 61-63, c1991. American Diabetes Association.

15) Pastore M, Bazzigaluppi E, Belloni C, et al. Six Months of Gluten- Free Diet Do Not Influence Autoantibody Titers, but Improve Insulin Secretion in Subjects at High Risk for Type 1 Diabetes. The Journal of Endocrinology & Metabolism 88(1): 162-165.2003.

16) Amin R, Murphy N, Edge J, et al. A Longitudinal Study of the Effects of a Gluten- Free Diet on Glycemic Control and Weight Gain in Subjects with Type 1 Diabetes and Celiac Disease. Diabetes Care, 25: 1117- 1122, July 2002.

17) Hansen D, Jacobsen B, Lund E, et al. Clinical Benefit Of a Gluten- Free Diet in Type 1 Diabetes Children With Screening- Detected Celiac Disease. Diabetes Care, 29: 2452- 2456, 11. Nov.2006.

18) Sharifi N, Khoshbaten M, Aliasgarzade A, et al. International Journal of Diabetes in Developing Countries. MedKnow Publications. Pvt. Ltd. 28.3 (Jul- Sept 2008): p95.

19) Peters U, Askling J, Gridley G, et al. Causes of Death in Patients With Celiac Disease in a Population- Based Swedish Cohort. Arch Intern Med. July 14, 2003; 163: 1566-1572.

20) Kumar V, Rajadhyaksha M, Wortsman J. Celiac Disease- Associated Autoimmune Endocrinopathies. Clinical And Diagnostic Laboratory Immunology. 8(4). 678-685. July 2001.