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Serum Immunoglobulin A Anti-Endomysial Antibody (IgA-EMA) and its Effectiveness in Screening for Celiac Disease in the Pediatric Population with Diabetes Mellitus 1

Lily McCauley

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Abstract

INTRODUCTION: Diabetes Mellitus Type 1 (DM 1) and celiac disease (CD) are both autoimmune diseases that are associated with the human leukocyte antigen (HLA)-DQ2 and human leukocyte antigen (HLA)-DQ8 genetic halotypes. Different geographical areas vary with prevalence of CD in populations with DM 1, ranging from 1.1% to 16.4%. Type 1 diabetes is a chronic autoimmune disease and accounts for approximately two thirds of all new diagnoses of diabetes in patients 19 years of age and younger, with a continue rise in incidence. Celiac disease is also an autoimmune disorder, and is characterized by intestinal villous damage caused by gluten ingestion. In the United States and Western Europe, the prevalence is approximately 1%. Individuals are susceptible to celiac disease on average, within 10 years of their DM 1 diagnosis. The incidence of celiac disease is increasing in those with type 1 diabetes because screening for CD has been made possible with the availability of non-invasive serological testing. Immunoglobulin A anti-endomysial antibody (IgA-EMA) has high sensitivity and specificity for celiac disease and has been proven to be effective in diagnosing atypical and latent CD. However, the “gold” standard for celiac diagnosis is the intestinal biopsy.

METHODS: The focus of this study was to review the current literature on all studies pertaining to IgA-EMA screening for celiac disease in the pediatric population with type 1 diabetes. The studies involved screening of type 1 diabetic patients for celiac disease with IgA-EMA and intestinal biopsies for those who tested positive for IgA-EMA.

RESULTS: The seven studies showed high prevalence of celiac disease in pediatric individuals with type 1 diabetes. Several studies also demonstrated that those who were initially negative for celiac disease later developed latent celiac disease.

CONCLUSION: IgA-EMA is an effective screening test for celiac disease in individuals with type 1 diabetes. The studies reported that due to the high prevalence of celiac disease in conjunction with type 1 diabetes, initial screening for celiac disease at diabetes onset is recommended and should be performed. They also stated that since seroconversion could occur, and patients could develop latent celiac disease, screening for celiac disease should also be performed after diabetes onset. How often and at what interval screening should be done is unanswered.

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Serum Immunoglobulin A Anti-Endomysial Antibody (IgA-EMA) and its Effectiveness in Screening for Celiac Disease in the Pediatric Population with Diabetes Mellitus

Lily McCauley

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2009

Faculty Advisor: Annjanette Sommers MS, PAC
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Lily McCauley was born in Canton, China. She immigrated to the United States when she was two years old. She attended Westminster College in Salt Lake City and graduated with a Bachelor’s degree in Psychology and a minor in Music. While in college, she worked as a Certified Nursing Assistant for a rehabilitation center. After Westminster, she went to Argosy University in Seattle to obtain a doctor in Psychology. While in Seattle, she worked as a residential counselor for Ruth Dykeman Children’s Center. At Argosy, she realized she wanted to study the entire human body rather than just focusing on the mind. After one year at Argosy, she decided to attend Portland State University and graduated with a Bachelor’s degree in General Science and minors in Biology and Chemistry. During her time at PSU, she volunteered at OSHU and Portland Veteran’s Medical Center. She applied to Pacific University and in 2007, she began her journey to become a Physician Assistant. After graduation she plans to work in the Portland area where she can stay close to family and friends.
Abstract

INTRODUCTION: Diabetes Mellitus Type 1 (DM 1) and celiac disease (CD) are both autoimmune diseases that are associated with the human leukocyte antigen (HLA)-DQ2 and human leukocyte antigen (HLA)-DQ8 genetic halotypes. Different geographical areas vary with prevalence of CD in populations with DM 1, ranging from 1.1% to 16.4%. Type 1 diabetes is a chronic autoimmune disease and accounts for approximately two thirds of all new diagnoses of diabetes in patients 19 years of age and younger, with a continue rise in incidence. Celiac disease is also an autoimmune disorder, and is characterized by intestinal villous damage caused by gluten ingestion. In the United States and Western Europe, the prevalence is approximately 1%. Individuals are susceptible to celiac disease on average, within 10 years of their DM 1 diagnosis. The incidence of celiac disease is increasing in those with type 1 diabetes because screening for CD has been made possible with the availability of non-invasive serological testing. Immunoglobulin A anti-endomysial antibody (IgA- EMA) has high sensitivity and specificity for celiac disease and has been proven to be effective in diagnosing atypical and latent CD. However, the “gold” standard for celiac diagnosis is the intestinal biopsy.

METHODS: The focus of this study was to review the current literature on all studies pertaining to IgA-EMA screening for celiac disease in the pediatric population with type 1 diabetes. The studies involved screening of type 1 diabetic patients for celiac disease with IgA- EMA and intestinal biopsies for those who tested positive for IgA- EMA. RESULTS: The seven studies showed high prevalence of celiac disease in pediatric individuals with type 1 diabetes. Several studies also demonstrated that those who were initially negative for celiac disease later developed latent celiac disease.

CONCLUSION: IgA-EMA is an effective screening test for celiac disease in individuals with type 1 diabetes. The studies reported that due to the high prevalence of celiac disease in conjunction with type 1 diabetes, initial screening for celiac disease at diabetes onset is recommended and should be performed. They also stated that since seroconversion could occur, and patients could develop latent celiac disease, screening for celiac disease should also be performed after diabetes onset. How often and at what interval screening should be done is unanswered. KEYWORDS: celiac disease, diabetes mellitus type 1, pediatric, children, adolescents, anti-endomysial antibody (EMA) and immunoglobulin A anti-endomysial antibody (IgA-EMA).
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To My Friends and Family: Thank you for all your encouragement and support. I am very lucky to have all of you in my life!
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Table I: Research Matrix of Journal Articles that Pertained to the Clinical Question
Table II: Validity Table of Journal Articles that Pertained to the Clinical Question

List of Abbreviations

DM 1.................................................................Diabetes Mellitus, Type I
IDDM.........................................................Insulin Dependent Diabetes Mellitus
CD.....................................................................................Celiac Disease
IgA- EMA.....................................................Immunoglobulin A Anti-Endomysial Antibody
(also refer to in studies as EMA)
DKA...............................................................Diabetic Ketoacidosis
HLA..............................................................Human Leukocyte Antigen
IEL...............................................................Intraepithelial Lymphocytes
Celiac Disease

Celiac disease (CD) is an autoimmune disease that is characterized by intestinal villous damage due to gluten ingestion. Gluten is found in wheat, barley, rye and possibly in oats. The ingestion of gluten involves T cells, lymphocytes and cytokines. The small intestinal epithelium is damaged by the cytokines, which trigger the release of the enzyme tissue transglutaminase (tTG), which then causes an increase in cytokine production. Inflammation, destruction of the intestinal villi, and crypt hypertrophy are caused by increased epithelial damage; an increase in plasma cells, macrophages, and lymphocytes; and the migration of lymphocytes to the surface of the epithelium. This cascade of inflammatory processes causes a lack of absorptive surface area and a decrease in the uptake of nutrients. However, the damage to the intestine can resolve itself when the gluten is removed.\(^1\)

In most pediatric cases celiac disease presents during the second year of life although the age of onset and severity are variable. The most common symptoms in the pediatric population are diarrhea, constipation, vomiting, abdominal pain, failure to thrive, anemia, and vitamin deficiencies.\(^2\) There are four categories of celiac disease: 1) classic celiac disease includes the symptoms mentioned previously, the presence of characteristic histological changes on small intestinal biopsy, and the resolution of mucosal lesions and symptoms upon withdrawal of gluten containing foods. 2) Atypical celiac disease involves pre-dominant extra-intestinal manifestations with few gastrointestinal symptoms. The diagnosis is similar in those with the classic disease and requires serological testing, biopsy of villous atrophy and symptom improvement on a gluten free diet. 3) In the case of silent/subclinical celiac disease these patients have a positive specific serologic test for celiac disease and biopsy evidence of villous atrophy, but no discernable symptoms. This condition is usually detected by screening of high
risk groups. After treatment with a gluten free diet many of these patients in retrospect recognize having had symptoms that they previously thought were normal.  

In the United States and Western Europe, the estimated prevalence of celiac disease is approximately 1%. The incidence continues to rise, which may be due to increased awareness and screening. According to the Celiac Disease Foundation, CD occurs in 5%-15% of the offspring and siblings of a person with celiac disease and in 70% of identical twin pairs. There is a 25% increased risk for developing celiac disease in family members who have any autoimmune disease.  

Type 1 Diabetes

Type 1 diabetes (DM 1) is a chronic autoimmune disease, previously called juvenile diabetes or insulin-dependent mellitus (IDDM). Type 1 diabetes is the most common type of diabetes in individuals younger than 40 years of age. Insulin is produced in the beta cells of the pancreatic islets and type 1 diabetes results from immunological damage to these insulin producing cells. In most people, this damage is gradual, occurring over months or even years. Symptoms of diabetes do not appear until approximately 90% of the pancreatic islets have been destroyed.  

Type 1 diabetes accounts for approximately two thirds of new diagnoses of diabetes in patients 19 years of age and younger in the United States. Worldwide, the incidence of type 1 diabetes varies, ranging from 0.1 to 37 per 100,000 children younger than 15 years of age. The reported incidence is 15 to 17 per 100,000 children in the United States. “The age of presentation has a bimodal distribution with peaks at 4 to 6 years of age and again between 10 and 14 years of age.”  

The risk of DM I increases significantly in close relatives of a patient of with type 1 diabetes. After the first twin develops diabetes 35%-50% of second identical twins develop diabetes. Approximately 6% of offspring or siblings with type I diabetes also develop type 1 diabetes. Exposure to one or more environmental agents seems to trigger an immune response in genetically
susceptible individuals that causes destruction of the pancreatic beta cells. According to several reports, these environmental factors such as viral infections, immunizations, diet (exposure to cow’s milk at an early age), vitamin D deficiency, perinatal factors (maternal age, history of preeclampsia, and neonatal jaundice), and low birth weight, increase the risk of type 1 diabetes. However, none of these associations have been confirmed and there are studies that are contradictory. 

The most common presentation of type 1 diabetes in childhood is hyperglycemia without acidosis. Hyperglycemia causes the following symptoms: polyuria, polydipsia, weight loss despite increased appetite, and lethargy. Children with type 1 diabetes that present with ketoacidosis (DKA) have similar but more severe symptoms than those without acidosis. For the diagnosis of DKA, hyperglycemia (blood glucose greater than 200 mg/dl) and metabolic acidosis, which is defined as a venous pH <7.3 and/or plasma bicarbonate less than 15 meq/L, must be present. Diabetic ketoacidosis is often the initial diagnosis of children with new onset type 1 diabetes and risk factors include: higher A1C levels and higher reported insulin requirements, female adolescents (with the highest risk in females over the age of 13 years old), children who are 13 years old, regardless of gender, who are underinsured and/or have a history of psychiatric disorders, and longer duration of diabetes. The earliest symptoms of DKA are similar to those in hyperglycemia. However, more severe symptoms include fatigue, weight loss, nocturia, daytime enuresis, and vaginal or cutaneous moniliasis (candidiasis of skin, manifested as eczema). If urinary losses are not replaced then hypovolemia may be severe. Hospitalization, rehydration, and insulin replacement therapy is important for children with DKA. Before the onset of clinical symptoms, some children will be diagnosed with type 1 diabetes. This occurs in children who have another close family member with DM 1 diabetes and who are being closely monitored. This is a silent presentation of DM and is the least common. The diagnosis of DM 1 is made when a clinician has a high index of suspicion. Although there is no current recommendation for pancreatic autoantibody screening, children with an affected close family member may undergo
Diabetes is diagnosed based upon one of the three detected abnormalities of glucose metabolism, a fasting plasma glucose greater than or equal to 126 mg/dL on at least two occasions, symptoms of hyperglycemia and a plasma glucose greater than or equal to 200 mg/dL, and an abnormal oral glucose tolerance test with a two hour blood glucose greater than 200 mg/dL.

Type I Diabetes and Celiac Disease

Through screening programs in children with type 1 diabetes, there is an increased prevalence of celiac disease compared with non-diabetic children. Different geographical areas vary in the prevalence of CD in populations with DMI, ranging from 1.1% to 16.4%. Both celiac disease and diabetes share an increased incidence of certain histocompatibility antigens such as human leukocyte antigen (HLA)-DQ2 and human leukocyte antigen (HLA) - DQ8, which seems to support the idea that both of these autoimmune diseases have a genetic pre-disposition. On average, within 10 years of their diabetic diagnosis, those who are susceptible will develop celiac disease. However, research has shown that late seroconversion occurs resulting in an underestimation of the prevalence of CD in type 1 diabetics.

Screening for celiac disease has been made possible by the availability of sensitive non-invasive serological testing. The immunoglobulin A anti-endomysial antibody (IgA-EMA) measurements, have high diagnostic specificity and sensitivity. This test has been proven to be effective in screening both atypical and latent forms of celiac disease. IgA deficiency occurs, however, in approximately 3% of the diabetic and celiac disease population and should be tested for because IgA deficiency can give false negative IgA-EMA results, which can cause a potential celiac disease diagnosis to be missed. Most DM 1 patients with celiac disease do not present with typical
gastrointestinal symptoms even in the presence of intestinal lesions. More common initial findings of CD in patients with DM 1 include unpredictable blood glucose measurements, recurrent episodes of hypoglycemia, reduced bone mineralization, and poor glycemic control and growth failure because of erratic intestinal absorption of nutrients. With intestinal biopsies, a wide range of histopathological abnormalities such as an increased number of intraepithelial lymphocytes to a completely atrophic mucosa can be found in the intestinal mucosa of diabetic children. Performing IgA-EMA screening in diabetic patients allows, for early identification, treatment of celiac disease, and the prevention of symptoms and a reduction in long-term morbidity. The patient should be referred to a gastroenterologist for confirmatory small bowel biopsy if the IgA-EMA test is positive. If the biopsy is positive for celiac disease then the patient should be placed on a gluten free diet. A registered dietitian, who has experience in caring for patients with both diabetes and celiac disease should provide, nutritional counseling because gluten free dietary substitutes are often high in carbohydrates. Identifying gluten free products with an acceptable amount of carbohydrates is important for management of patients with both diabetes and celiac disease.

Due to the prevalence of celiac disease and its impact on type 1 diabetes, it is recommended that all children with DM 1 diabetes be screened for celiac disease. If IgA-EMA is negative, then patients should be rescreened. If the child develops symptoms suggestive of celiac disease, or demonstrates poor growth or weight loss, screening should be performed earlier. Although there are several blood tests used in the screening of celiac disease, this paper focuses on the immunoglobulin anti-endomysial antibody (IgA-EMA) due to its high specificity and sensitivity. This paper will also focus and address the question of how often it is necessary to screen for celiac disease after the onset of diabetes mellitus 1 and if screening is necessary if initial IgA-EMA test is negative.
Materials and Methods

A comprehensive literature search was compiled using the keywords: diabetes mellitus 1, celiac disease, adolescents, children, pediatric, anti-endomysial antibody (EMA) and immunoglobulin A anti-endomysial antibody (IgA-EMA) on Ovid-Medline, CINAHL, MD Consult, Evidence Based Medicine Reviews Multifile, UpToDate Inc., and Current Diagnosis and Treatment in Pediatrics. Literature from 1998 to present was reviewed and weighted towards importance in answering the clinical question. The results were then compiled and analyzed. The inclusion criteria were all relevant English language articles that aided in explaining the importance of immunoglobulin A- anti-endomysial antibody, screening for celiac disease in the pediatric population with type 1 diabetes. Exclusion criteria included articles that discussed other autoimmune disorders, discussion of the adult population, and studies that offered other screening tests besides IgA-EMA.

Results

A total of seven English language studies were published between 1998 and 2008, addressing the increased prevalence of celiac disease in the pediatric population with type 1 diabetes. All of these studies utilized in this systematic reviewed performed immunoglobulin A anti-endomysial antibody (IgA-EMA) screening in the diabetic pediatric population and if the IgA-EMA was positive, intestinal biopsies were performed. Each article was reviewed and graded on the following criteria: sample size, whether or not biopsy results were affected based on IgA-EMA results, and methods/ criteria used to diagnosis celiac disease.

Between October 1995 and April 1997, Fraser-Reynolds et al. performed a prospective cohort study to determine if the serological marker, the immunoglobulin A anti-endomysial antibody (IgA-EMA) could be used to screen for celiac disease in North American children with type 1 diabetes. The subjects included 236 diabetes clinical patients (two additional diabetic patients were diagnosed with celiac disease before this study and were not included) and 56 gastrointestinal clinic patients, who
underwent intestinal biopsy for suspected malabsorption. Total IgA and IgA-EMA assays were performed. Diabetics were asked to undergo biopsies if they were positive for IgA-EMA. An experienced histopathologist, who was blinded to patient data, assessed the tissue sections for celiac disease using the following abnormalities, villous atrophy crypt hyperplasia, an increased in intraepithelial lymphocytes (IEL) and chronic inflammation in the lamina propria. Celiac disease was defined as an increased number of intraepithelial lymphocytes with associated subtotal villous atrophy or total villous atrophy. None of the diabetic patients were IgA deficient and 19 of the 236 diabetic patients were positive for IgA-EMA (8%). 17 patients were biopsied (2 refused), 12 had celiac disease and 3 out of the 12 patients were symptomatic (1 had loose stools and 2 had frequent stools and bloating). The estimated prevalence of celiac disease for diabetic patients in this study was 5.1% (12 /236). Three of the 56 gastrointestinal patients were IgA-EMA positive and had biopsies diagnostic of celiac disease. Another three individuals were found to be IgA deficient and one out of the three IgA deficient patients had celiac disease. Of the 50 IgA sufficient and IgA-EMA negative patients, one had celiac disease and 49 did not. The estimated prevalence of celiac disease for the gastrointestinal patients was 8.9% (5/56). Sensitivity was calculated by dividing the number of patients with a jejunal biopsy indicative of celiac disease, who were IgA-EMA positive, by the total number of patients with a jejunal biopsy indicative of celiac disease multiplied by 100. Specificity was calculated by dividing the number of patients with a normal jejunal biopsy and a negative IgA-EMA test by the total number of all the patients with a normal jejunal biopsy, multiplied by 100. The IgA-EMA test in this study had a sensitivity of 94% and a specificity of 91%.One of the 17 IgA-EMA positive diabetic patients underwent multiple biopsies. The first biopsy was normal. However, 6 months later a second biopsy was performed because of erratic blood glucose control and persistent post-prandial abdominal discomfort. The second biopsy showed total villous atrophy. This increased the initial prevalence of 5.1% to 5.5%. There was no difference in the mean age of onset of type 1 diabetes in the celiac group
versus the non-celiac group. Also, there was no difference in the mean duration of diabetes in the patients with celiac disease versus those who did not have celiac disease.  

Aktay et al. conducted a prospective cohort study between December 1996 and December 1998 to determine the prevalence and clinical presentation of celiac disease in children and adolescents with juvenile diabetes in Wisconsin, USA, using the serum immunoglobulin A endomysial antibody (IgA-EMA) as a screening test. In this study 218 patients with diabetes and 117 age and gender matched control patients were tested for IgA-EMA. Patients who were positive for IgA-EMA were offered a small bowel biopsy. Histopathologic examination was performed by a pediatric pathologist who made the diagnosis of celiac disease based on the following criteria, villous atrophy, inflammation in the lamina propria with increased intraepithelial lymphocytes (IEL) and hyperplasia of the crypts. Biopsy specimens were classified as having partial or total villous atrophy. Seventeen of the 218 diabetic patients (7.7%) had positive IgA-EMA. All control patients were negative for IgA-EMA. Small bowel biopsies were performed in 14 diabetic patients. Ten of the patients had villous atrophy and were newly diagnosed with celiac disease. The prevalence of CD in DM 1 patients in this study was 4.6% (10/218). Of the ten newly diagnosed patients with CD, one patient who had mild villous architectural alterations and increased intraepithelial lymphocytes had total villous atrophy on a second biopsy. Two patients, who were not diagnosed with celiac disease, had minor histological changes such as increased intraepithelial lymphocytes, focal acute inflammation, and mild architectural change of villi without villi atrophy. The other two patients had normal mucosal morphologic features. One patient who had negative villi atrophy had a repeat biopsy two years later, which showed villous atrophy. This increased the initial prevalence of CD in type 1 diabetics from 4.6% to 5.0%.  

Barera et al. conducted a six year prospective longitudinal study, to investigate the prevalence of celiac disease in a large cohort of children and adolescents at the onset of type 1 diabetes, and the occurrence of new cases during a six year follow up. From January 1993 to January 1999, 274 patients
with new onset type 1 diabetes were recruited from Northern Italy. One patient had a diagnosis of celiac disease before the onset of type 1 diabetes and was excluded from the study. All patients were tested for serum IgA and, if patients were IgA deficient, then they were tested for IgG-antiendomysium and IgG-antigliadin antibodies. All 273 eligible patients were tested for IgA-EMA at the onset of type 1 diabetes and annually up to 6 years. Patients with positive results or two consecutive weak positive results were considered appropriate for jejunal biopsy. A pathologist, who was blinded to IgA-EMA results, examined the biopsy specimens according to the mucosal change described by the Marsh classification. The infiltrative (type 1) lesion comprises normal mucosa architecture in which the villous epithelium is markedly infiltrated by small non-mitotic intraepithelial lymphocytes (IEL). The hyperplastic (type 2) lesion is similar to the type 1 lesion but with the addition of enlarged crypts the epithelium of which, like the villi, is also infiltrated by intraepithelial lymphocytes. The destructive (type 3) lesion is characterized by some degree of villous atrophy, with inflammation and hyperplastic crypts, and is the classic lesion associated with celiac disease. The diagnosis of CD was considered the histological demonstration of the hyperplastic or destructive mucosal lesions, type 2 or 3. Of the 273 patients, two were IgA deficient and IgG-antiendomysium and IgG-antigliadin antibody assays tested normal in both. Fifteen individuals (5.5%) tested positive with the IgA-EMA assay. Nine presented IgA-EMA assay positive and six were only weakly positive. Five of the six patients with weak IgA-EMA reactivity were negative at the second assay and the intestinal biopsy was not performed. A total of ten intestinal biopsies were performed. Nine individuals had hyperplastic or destructive lesions consistent with celiac disease. The overall prevalence of CD in these 274 patients with new onset type 1 diabetes was 3.6%, of which one case was already known and nine were detected by screening. Within a four year follow up 12 more patients with a negative IgA-EMA antibody test at diabetes onset tested positive. Ten biopsies were performed and seven patients were found to have celiac disease. The cumulative prevalence of patients with at least 1 positive IgA-EMA test was 9.9% (27/273) and
cumulative prevalence of the entire cohort of patient patients with biopsy proven celiac disease was 6.2% (10 out of 274). The age of type 1 diabetes onset was not different between patients who had celiac disease and those who did not. Therefore, the study determined the age at onset of type 1 diabetes was not a predictor of celiac disease development. Within 6 years, the risk of developing at least one positive IgA-EMA assay was 13.8% and a biopsy confirmed celiac disease was 8.3%. The prevalence of CD in type 1 diabetics increased initially from 3.6% to 8.3% in six years. \(^{10}\)

Crone et al. conducted a prospective cohort study to test the hypothesis that immunoglobulin A anti-endomysial antibody (IgA-EMA) positivity can occur at any time during the course of diabetes. All patients from the diabetic mellitus outpatient clinic between 1993 and 2001 at the University Children’s Hospital of Vienna were screened for celiac disease with IgA-EMA. Total IgA levels were measured in all patients. In one patient with IgA deficiency, screening with IgG-EMA was performed. All patients with positive IgA-EMA underwent small bowel biopsy, and the specimens were analyzed according to the Marsh criteria. Follow up data for at least three years, with least two IgA-EMA measurements, were available for the 157 diabetic patients. For 37 of 157 patients, the first IgA-EMA measurement was performed on manifestation of DM 1. In the rest of the patients the first IgA-EMA measurement was taking during the course of DM 1. In 16 of 157 screened patients with diabetes, IgA-EMA was positive. In group one, 8 out of 37 patients were positive for IgA-EMA (21.6%) and six of them had manifestations of diabetes. Biopsy results of one patient showed normal mucosa, in another patient increased intraepithelial lymphocyte counts, indicating a potential for CD, were seen and in four other patients, partial to total villous atrophy, celiac disease, was observed. The prevalence of celiac disease at this initial testing was 10.8% (4/37). Eleven to 12 months after first screening, two additional patients tested positive for IgA-EMA. One patient had a normal mucosa biopsy and the other had total villous atrophy (celiac disease). The prevalence increased from 10.8% to 13.5% (5/37). In group two, 8 out of 120 patients tested positive for IgA-EMA (6.7%). Biopsy results showed normal
mucosa in four patients and partial to villous atrophy, celiac disease, in four other patients. The prevalence of biopsy proven celiac disease was 3.3% (4 out 120).  

In 2002, Mankai et al. conducted a prospective cohort study to evaluate the frequency of celiac disease among Tunisian children with diabetes mellitus 1. The study was conducted on 205 children with DM 1 from four hospitals at the center of Tunisia. All patients were screened for celiac disease by determination of immunoglobulin IgA anti-endomysial antibodies (IgA-EMA). IgA-EMA was positive in 17 out of 205 children with DM 1 (8.3%). In 13 out of 17 IgA-EMA positive patients, duodenal biopsies were performed (the parents of the 4 remaining IgA-EMA positive children refused biopsy). The biopsy specimens were read by two pathologists, who were blinded to patient identity and the intestinal mucosa was classified according to the Marsh criteria. 11 out the 13 patients were found to have confirmed celiac disease. Eight patients showed a total villous atrophy and three patients showed partial villous atrophy. All 11 patients had elevated counts of intraepithelial lymphocytes. The other two patients showed a normal histological picture with a normal number of intraepithelial lymphocytes. Only three of the 11 patients had celiac signs or symptoms. Prevalence of celiac disease in type 1 diabetics in this study was 5.4% (11/205).  

Salardi et al. conducted a longitudinal study to verify whether the prevalence of the association between type 1 diabetes and celiac disease has changed in the last 18 years and whether the immunological onset of celiac disease differs among children with type 1 diabetes. In 1987, a prospective evaluation of celiac disease related antibodies, in 331 DM 1 pediatric patients was started. 180 children were diagnosed with DM1 between 1987-1994 and 151 children were diagnosed with DM1 between 1995-2004. All of the patients underwent immunological evaluation when diabetes was diagnosed and every six to twelve months thereafter, for 18 years. All patients were tested for immunoglobulin A anti-endomysial antibodies (IgA-EMA) prospectively from 1994 to 2004, and retrospectively, from 1987 to 1993. Before 1994, sensitivity was 95% and specificity was 98%. After
1994, sensitivity was 98% and specificity was 100%. The diagnosis of celiac disease was confirmed by an intestinal biopsy with a gastroduodenoscopy and multiple biopsies. Histological abnormalities were graded according to the Marsh classification. Of the 331 diabetic children enrolled in the study, two were affected by celiac disease before being diagnosed with diabetes whereas 29 (8.8%) were found to be positive on the IgA-EMA assay upon the diagnosis of diabetes or thereafter. 23 patients underwent biopsy (six did not undergo biopsy because two had borderline IgA-EMA positivity and four became negative with IgA-EMA retesting). 18 out of 23 had typical lesions and the rest of the patients had normal mucosa. The initial prevalence of celiac disease in type 1 diabetic children in this study was 6.02%, 20 patients, 2 already known and 18 discovered at screening, out of 331. In two of the five patients who were initially negative a second biopsy was carried out at 1 and 4.5 years respectively, following the onset of clinical symptoms, and showed typical celiac lesions whereas the three other patients were negative for IgA-EMA during post-biopsy follow up of two to eight years did not. Therefore, there were 3 false positives (13%) and a total of 22 cases, 20 at initial biopsy and 2 more at follow up, of proven biopsy celiac disease. In this study the overall prevalence of celiac disease in type 1 diabetic children increased initially from 6.02% to 6.6%. However, the 22 cases of celiac disease were not distributed evenly throughout the observation period rather, the study noted a sudden dramatic increase in celiac disease in 1995. The observation period was divided into two parts, before 1994 and after 1994 and the prevalence of celiac disease was calculated separately in two parts. Between 1987 and 1994, among the 180 children with newly diagnosed diabetes, six were affected with celiac disease, making the prevalence rate of CD before 1994 3.3% (6/180). Between 1995 and 2004, 151 new cases of diabetes were diagnosed and 16 were affected with celiac disease, making the prevalence rate of CD after 1994 10.6% (16/151). In 2004, Baptista et al. conducted a prospective cohort study to determine the prevalence of celiac disease in Brazilian children and adolescents with type 1 diabetes. 104 pediatric patients with
DM 1 and 105 healthy pediatric patients, who were used as a control group, were tested for the presence of IgA anti-endomysial antibody (IgA-EMA). Total serum IgA levels were measured to detect possible serum IgA deficiency in all patients. In patients with IgA deficiency, IgG-EMA was tested. Small bowel biopsies were offered in patients who were IgA-EMA positive. Biopsies were analyzed according to a modified Marsh classification. Celiac disease diagnosis was made by the following criteria: villous atrophy, elevated intraepithelial lymphocytes (IEL) count, and hyperplasia of the crypts. Among the 104 patients with DM 1, nine patients were positive for IgA-EMA (8.7%). Three diabetic patients were IgA deficient but since they were negative for IgG-EMA, they were not excluded from the study. All of the healthy controls were negative for IgG-EMA. Two of the nine IgA-EMA patients had an increased IEL count with subtotal and partial villous atrophy respectively. Three other patients had partial villous atrophy with non-elevated IEL counts but were considered as having celiac disease. The remaining four patients had normal histology. In this study, the overall results show a prevalence of celiac disease of 4.8% (5/104).

Discussion

In this systemic review, only prospective studies were found. No randomization studies were conducted because celiac disease could not be randomly assigned to patients. The studies utilized a select group of individuals with type 1 diabetes rather than the entire population of diabetics and the subjects were not randomly selected, therefore only an estimated prevalence of celiac disease could be reported. The studies each addressed a large sample of diabetic patients (at least 100 patients per study) and showed a prevalence of celiac disease in the DM 1 population to be greater than 3%.

In all of the studies, all patients with a positive IgA-EMA were offered biopsies. All of the studies described similar methods used to screen for IgA-EMA and biopsies for celiac disease, so there was no difference between the studies in these areas. The biopsies were performed after the IgA-EMA results were obtained so the biopsy results were not affected by the IgA-EMA. In fact, three out of the
seven articles mentioned that the histopathologists were blinded to the results of the IgA-EMA, which also supports the idea that biopsy results were not affected by the IgA-EMA. All of the articles used the Marsh criteria in some form, in the diagnosis of celiac disease; therefore there were no differences in diagnosing celiac disease on biopsy. However, some patients refused biopsies after testing positive for IgA-EMA. The studies conducted by Aktay et al. and Mankai et al. had patients who refused biopsies, resulting in it being impossible to reach a definitive conclusion as to whether or not these patients had celiac disease.

All of the studies tested IgA-EMA on patients with diabetes type 1 and some studies included a control group. In the study conducted by Fraser-Reynolds et al. a control group of non-diabetic gastrointestinal patients was used, which showed a prevalence of celiac disease to be 8.9% compared to the diabetic 1 population which was 5.1%. This higher prevalence of celiac disease may be due to the fact that a smaller specific population, experiencing gastrointestinal symptoms was being tested. This was a good comparison because it showed that, although there was an increased prevalence of celiac disease in the population with DM 1 it is not as great as the population, which is non-diabetic but is experiencing gastrointestinal complaints. Aktay et al. tested IgA-EMA on gender matched control patients and all control patients tested negative. This comparison makes a strong point that having DM 1 increases the prevalence of positive IgA-EMA. The study conducted by Baptista et al. also used a control group, which tested negative for IgA-EMA, therefore emphasizing the point that having DM 1 increases an individual’s chance of developing a positive IgA-EMA.

Compared to the general population, IgA deficiency is more common in patients with celiac disease and can lead to false negative results in the IgA-EMA. The studies conducted by Aktay et al., Mankai et al., and Salardi et al. did not test for IgA deficiency so the results of the IgA-EMA in these studies could be falsely negative and the actual prevalence of positive IgA-EMA could be higher than was stated.
The studies that performed follow up with retesting of IgA-EMA seem to show that it is possible for an individual with a negative IgA-EMA to sero-convert to a positive IgA-EMA. The same is true of the biopsy; an individual who was initially negative for celiac disease may later develop celiac disease and demonstrate a positive biopsy at follow up. This was demonstrated in the study conducted by Fraser-Reynolds et al.; one of the IgA-EMA positive patients with an initial normal biopsy underwent a second biopsy six months later, which confirmed celiac disease, increasing the prevalence of celiac disease from 5.1% to 5.5%. Aktay et al. demonstrated this idea as well in their study when one of the patients, who initially had a negative biopsy, had a repeated biopsy two years later, which indicated villous atrophy, increasing the prevalence of celiac disease from 4.6% to 5.0%. In the study conducted by Barera et al. the prevalence of celiac disease in these diabetic individuals was 3.6%. Within four years of follow up, the estimated prevalence of CD increased to 6.2%, and after six years the prevalence of CD increased even higher to 8.3%. This study indicated that patients who had initially been IgA-EMA negative could become IgA-EMA positive a few years later. This study demonstrates that being negative IgA-EMA initially does not prevent an individual from developing positive IgA-EMA later on, and that it is possible for an individual who is IgA-EMA negative to develop celiac disease. In the study by Crone et al. the initial prevalence of celiac disease at the onset of diabetes was 10.8%. One year later, a patient who initially tested negative for IgA-EMA became positive and the biopsy demonstrated celiac disease; increasing the prevalence of celiac disease to 13.5%. This increase in prevalence rate showed that seroconversion occurred and a negative IgA-EMA does not rule out the development of celiac disease later on. The study conducted by Salardi et al. showed an initial prevalence of celiac disease to be 6.2% but at follow up two patients, who were initially negative at biopsy had a second biopsy, which showed celiac disease to be present and increased the prevalence to 6.6%. This also supports the idea the seroconversion can occur in those who initially had a negative biopsy.
These studies that performed follow up did not follow everyone who was negative IgA-EMA to see if they developed positive IgA-EMA later on, therefore the estimated prevalence rate of positive IgA-EMA could actually be higher than was stated if follow up was performed. This is true of the biopsy as well; not all patients who had a negative biopsy initially received a follow up biopsy so prevalence of celiac disease could also be underestimated.

Some of the studies stated that age at onset and duration of diabetes does not affect the prevalence rate of celiac disease but this may not be the case. In fact, the study conducted by Barera et al. mentioned that incidence of celiac disease increased with the duration of diabetes because patients were screened at several times rather than just at one point. Also the study conducted by Mankai et al. stated that DM 1 patients with positive IgA-EMA had earlier onset of DM 1 compared to those who were negative for IgA-EMA. The studies that performed follow up on patients demonstrated that those who were initially negative at screening with IgA-EMA later seroconverted to positive IgA-EMA and developed latent celiac disease. Patients who developed latent celiac disease had a longer duration of diabetes, which could in fact be the cause of seroconversion but this issue was not addressed and should be in future studies.

Since there seems to be a link between diabetes and celiac disease along with the possibility of seroconversion all the studies recommended that initial screening for celiac disease is necessary for those with DM1 and state the importance of follow up screening. However, the studies conducted by Barera et al., Crone et al., and Mankai et al. were the only studies that mentioned at what interval screening should be performed after diabetes diagnosis. The term “several years” is vague and does not give a definitive answer as to exactly how often testing should be performed. The recommendation of annual screening helps determine at what interval screening should be performed but also does not address for how many years. The range of two to five years is wide and variable, which does not give a definite screening schedule. The questions that still need to be addressed are “at what intervals and for
how long should DM 1 patients be screened and biopsed for celiac disease?” The studies also do not mention the cost of the screening or the biopsies so affordability of the tests is undetermined. If the testing for IgA-EMA and biopsies are costly, frequent testing and follow up may not be possible due to the high cost.

**Conclusion**

There seems to be a link between celiac disease and diabetes type 1. Having DM 1 increases an individual’s chance of a positive IgA-EMA result and his risk of developing celiac disease. Compared to the population who is experiencing gastrointestinal symptoms and having problems with malabsorption, the risk of CD in the DM 1 patient is not as great, but compared to the general population without any symptoms, the risk is greater. Therefore, it is important to screen for celiac disease in the DM 1 patient especially if they are experiencing gastrointestinal symptoms. Due to this link and the possibility of seroconversion, initial screening of celiac disease in the DM 1 population and follow up with retesting, is recommended. Testing patients for celiac disease at more than one point in their disease may help better answer the question as to whether or not having diabetes longer increases the individual’s risk of developing celiac disease. It is also important to test all patients for IgA deficiency to make the IgA-EMA results more valid. Without testing for this deficiency, the IgA-EMA results could be falsely negative, therefore underestimating the prevalence of positive IgA-EMA results. If an individual is IgA deficient and is not tested, then a biopsy is not performed because it is thought that they are IgA-EMA negative, and a possible celiac disease diagnosis can be missed. Detecting celiac disease early is important in the treatment of the disease. By catching the disease earlier in its course, morbidity issues such as vitamin deficiencies, poor glucose control and growth failure could be prevented.

The studies show that the initial screening for celiac disease in DM 1 patients is important but the question at what interval and for how long follow up should be performed still needs to be
addressed. The cost of the biopsy and whether or not insurance will pay for follow up testing needs to be looked into because frequent testing may not be available to patients if the tests are not affordable.
Table 1. Research Matrix of Journal Articles that Pertained to the Clinical Question

<table>
<thead>
<tr>
<th>Author / Journal Title</th>
<th>Year Published</th>
<th>Patients / Population</th>
<th>Positive IgA-EMA</th>
<th>Positive Biopsy</th>
<th>Study Type</th>
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<tbody>
<tr>
<td>Fraser-Reynolds, K.A. et al. / Use of IgA-EMA to screen for celiac disease in North American children with type 1 diabetes</td>
<td>1998</td>
<td>236 DM 1 patients 56 GI patients</td>
<td>19 DM 1 patients (8%) 3 GI patients (5.4%)</td>
<td>12 DM 1 patients (5.1%) 5 GI patients (8.9%)</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td>Aktay, A.N. et al. / The Prevalence and Clinical Characteristics of Celiac Disease in Juvenile Diabetes in Wisconsin / Journal of Pediatric Gastroenterology and Nutrition</td>
<td>2001</td>
<td>218 DM 1 patients 117 control patients</td>
<td>17 DM 1 patients (7.7%) All controls were negative</td>
<td>10 DM 1 patients (4.6%) initially 11 DM 1 patients (5.0%) at follow up</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td>Barera, G. et al. / Occurrence of Celiac Disease after onset of Type 1 Diabetes: a 6- year prospective longitudinal study / Pediatrics</td>
<td>2002</td>
<td>274 DM 1 patients</td>
<td>15 DM 1 patients (5.5%) initially In 4 yrs - 9.9% In 6 yrs - 13.8%</td>
<td>10 DM 1 patients (3.6%) initially In 4 yrs -6.2% In 6 yrs - 8.3%</td>
<td>Prospective longitudinal</td>
</tr>
<tr>
<td>Crone, J. et al / Prevalence of Celiac Disease and Follow up of EMA in children and adolescents with Type I diabetes/ Journal of Pediatric Gastroenterology and Nutrition</td>
<td>2003</td>
<td>157 DM 1 patients (37 were at the onset of diabetes and 120 were during the course of diabetes)</td>
<td>8 DM 1 patients at onset of diabetes (21.6%) 8 DM 1 patients in the course of diabetes (6.7%)</td>
<td>Onset: 4 DM 1 patients (10.8%) initially. 5 DM 1 (13.5%) patients at follow up Duration: 4 DM 1 patients (3.3%)</td>
<td>Prospective cohort</td>
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<tr>
<td>Mankai, A. et al / Screening by anti-endomysium antibodies for celiac disease in Tunisian children with type 1 diabetes mellitus/Gastroenterology Clinic and Biology</td>
<td>2007</td>
<td>205 DM 1 patients</td>
<td>17 DM 1 patients (8.3%)</td>
<td>11 DM 1 patients (5.4%)</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td>Salardi, S. et al / Prevalence of Celiac Disease with Type I DM Increased in the Mid-1990s: An 18 year Longitudinal Study Based on Anti-endomysial antibodies/Journal of Pediatric Gastroenterology and Nutrition</td>
<td>2008</td>
<td>331 DM 1 patients (180 diagnosed before 1994 and 151 diagnosed after 1994)</td>
<td>29 DM 1 patients (8.8%)</td>
<td>20 DM 1 patients (6.02%) initially 22 DM 1 patients (6.6%) at follow up 6 DM 1 patients (3.3%) before 1994 and 16 DM 1 patients (10.6% after 1994)</td>
<td>Prospective &amp; Retrospective Longitudinal</td>
</tr>
<tr>
<td>Baptista, M.L. et al. / Prevalence of Celiac Disease in Brazilian Children and Adolescents with Type 1 Diabetes Mellitus/Journal of Pediatric Gastroenterology and Nutrition</td>
<td>2005</td>
<td>104 DM 1 patients 105 control patients</td>
<td>9 DM 1 patients (8.7%) All controls were negative</td>
<td>5 DM 1 patients (4.8%)</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td>Author/ Title/ Journal</td>
<td>Was there an independent blind comparison with a reference standard?</td>
<td>Was the diagnostic test evaluated in an appropriate spectrum of patients (like those in whom it may be used in practice?)</td>
<td>Was the reference standard applied regardless of the diagnostic test result?</td>
<td>Were the methods of the test described in sufficient detail to permit replication?</td>
<td>Validity Score</td>
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<tr>
<td>Fraser-Reynolds, K.A. et al./Use of IgA-EMA to screen for celiac disease in North American children with type 1 diabetes</td>
<td>Yes. The reference standard, the biopsy was performed on those who were positive for IgA-EMA. The IgA-EMA results were not affected by the biopsy results because the IgA-EMA was performed prior to the biopsy. Pathologist was unaware of pt’s information.</td>
<td>Yes. The diagnostic test, IgA-EMA was performed on all patients with DM I along with comparison group of GI pts. The IgA-EMA was used to determine if those who have DM I were at a greater risk of developing CD compared to those who did not have DM I but had GI complaints.</td>
<td>Cannot tell because in biopsies were performed in only DM I pts with positive IgA-EMA. But in the GI pts with negative IgA-EMA biopsies were performed.</td>
<td>Yes. The IgA-EMA, biopsy, histology and statistical analysis were discussed in detail.</td>
<td>3</td>
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<tr>
<td>Aktay, A.N. et al. / The Prevalence and Clinical Characteristics of Celiac Disease in Juvenile Diabetes in Wisconsin / Journal of Pediatric Gastroenterology and Nutrition</td>
<td>Yes. The reference standard was the biopsy, which were offered for those who had a positive IgA-EMA. The results of the IgA-EMA were not affected by the biopsy because the IgA-EMA was performed beforehand.</td>
<td>Yes. The diagnostic test, IgA-EMA was performed on all patients with DM I and the match control patients. The IgA-EMA was used to determine if DM I pts are a greater risk for CD compared to the control pts.</td>
<td>No. The biopsy was not performed unless the IgA-EMA was positive and for 3 of the positive pts. refused the biopsy.</td>
<td>Yes. The IgA-EMA, biopsy and pathology was discussed in detail.</td>
<td>3</td>
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<tr>
<td>Barera, G. et al/ Occurrence of Celiac Disease after onset of Type 1 Diabetes: a 6- year prospective longitudinal study / Pediatrics</td>
<td>Yes. The reference standard was the biopsy which was performed with a positive IgA-EMA. The results of the IgA-EMA were not affected by the biopsy because the IgA-EMA was performed before the biopsy. Pathologist was blinded to IgA-EMA results.</td>
<td>Yes. The diagnostic test IgA-EMA was used to determine if those who have DM I are at risk for developing CD. Follow up studies were also done to determine if duration of DM I increases the risk of CD.</td>
<td>No. The biopsy was performed only in those who had a positive IgA-EMA.</td>
<td>Yes. This article went into great detail of how the IgA-EMA and biopsies along with the histology were performed.</td>
<td>3</td>
</tr>
<tr>
<td>Crone, J. et al / Prevalence of Celiac Disease and Follow up of EMA in children and adolescents with Type 1 diabetes/ Journal of Pediatric Gastroenterology and Nutrition</td>
<td>Yes. The reference standard was the biopsy which was performed with a positive IgA-EMA. The results of the IgA-EMA did not affect the results of the biopsy because the IgA-EMA was performed beforehand.</td>
<td>Yes. The diagnostic test IgA-EMA was used to determine if having DMI puts an individual at risk for developing CD. Follow up studies were also done to determine if prevalence of CD was greater during the course of DMI than the onset.</td>
<td>No. The biopsy was performed only in those who had a positive IgA-EMA.</td>
<td>Yes. The article discussed how the IgA-EMA and biopsy were performed in detail. Histology of the biopsy was discussed as well.</td>
<td>3</td>
</tr>
<tr>
<td>Study</td>
<td>Reference Standard</td>
<td>Diagnostic Test</td>
<td>Biopsy Results</td>
<td>Methodology</td>
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<tr>
<td>Mankai, A. et al/Screening by anti-endomysium antibodies for celiac disease in Tunisian children with type 1 diabetes mellitus/Gastroenterology Clinic and Biology</td>
<td>Yes. The reference standard, the biopsy was performed for pts who had a positive IgA-EMA. The results of the IgA-EMA were not affected by the biopsy results because the IgA-EMA was performed first. The pathologists were blinded of the IgA-EMA results as well.</td>
<td>Yes. The IgA-EMA was performed on all patients with DM I to determine if having DM increases an individual’s risk of developing CD.</td>
<td>No. The biopsy was not performed unless the pt. had a positive IgA-EMA. 4 of the positive IgA-EMA pts refused biopsies.</td>
<td>Yes. The IgA-EMA, biopsy, histology and statistical analysis were explained detail.</td>
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<tr>
<td>Salardi, S. et al/Prevalence of Celiac Disease with Type I DM Increased in the Mid-1990s: An 18 year Longitudinal Study Based on Anti-endomysial antibodies/Journal of Pediatric Gastroenterology and Nutrition</td>
<td>Yes. The reference standard, biopsy was performed on those were positive for IgA-EMA. The IgA-EMA results were not affected by the biopsy results because the IgA-EMA was performed beforehand. Reproducibility of the test (performed in double blind) was high.</td>
<td>Yes. The diagnostic test was performed on all patients with DM I. Follow up study was performed to determine if longer onset of DM I increases risk of developing CD.</td>
<td>No. Biopsies were performed with only positive IgA-EMA and 2 of the positive pts. refused the biopsies.</td>
<td>Yes. The IgA-EMA, biopsy and histology methods along with the statistical analysis were discussed in detail.</td>
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<tr>
<td>Baptista, M.L. et al/Prevalence of Celiac Disease in Brazilian Children and Adolescents with Type 1 Diabetes Mellitus/Journal of Pediatric Gastroenterology and Nutrition</td>
<td>Yes. The reference standard, the biopsy was performed for pts., who had positive IgA-EMA. The results of the IgA-EMA were not affected by the biopsy because the IgA-EMA was performed first.</td>
<td>Yes. The IgA-EMA was performed in all pts to determine if DM I pts. have a greater risk of developing CD compared to the controls.</td>
<td>No. The biopsy was performed only on those with positive IgA-EMA results.</td>
<td>Yes. The IgA-EMA, biopsy, and statistical analysis methods were discussed in detail.</td>
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References


