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RESEARCH ARTICLE

Prevalence of celiac disease in children with insulin dependent diabetes mellitus in Taif governorate KSA

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Abstract

Celiac disease is caused by a complex immunological response provoked by grain protein in susceptible people. The prevalence of CD in children with IDDM ranges between 1.3 and 12% throughout the world and may contain a high proportion of clinically asymptomatic and atypical cases. The main role of the serological tests in clinical practice is in screening patients with diseases associated with CD and who may have atypical or silent forms of CD, in order to avoid an unnecessary biopsy.

Introduction

Celiac disease is a gliadin induced enteropathy of the intestinal mucosa arising in predisposed subjects as the result of sensitivity to ingested gluten in genetically susceptible people with the subsequent immune reaction leading to small bowel inflammation and villous atrophy.(1)

Celiac disease, the most common food sensitive enteropathy in humans, can be defined as a permanent intolerance to gluten that results in damage consists of mucosal inflammation and loss of absorptive surface area and is manifested by a broad spectrum of symptoms and nutritional deficiencies.(2)

Celiac disease has a worldwide distribution, but the exact incidence and prevalence rates are difficult to establish because of a significant number of asymptomatic cases.(3). The pathogenesis of Celiac disease involves the interaction of the water-insoluble protein moiety "gluten" of certain cereal grains in the mucosa of the small intestine.(4).

The prevalence of celiac disease in patients with type I diabetes is approximately 20 times higher than in the general population. Sixty percent of cases are already present at diabetes onset, mostly undetected, but an additional 40% of patients develop celiac disease a few years after diabetes onset.(5).

Gliadin has been separated into four major fractions: alpha, beta, gamma and omega. There is agreement that alpha gliadin is toxic to patients with celiac disease but there is controversy whether all fractions are toxic.(6).Evidence suggests that; hereditary factors play a significant role, as Celiac disease is diagnosed in around 10% of first degree relatives of an individual with celiac disease.(7). Celiac disease could be manifested by a previously unappreciated range of clinical presentations including the typical malapsorption syndrome (chronic diarrhea, weight loss, abdominal distention) and a spectrum of symptoms potentially affecting any organ system.(8)

Untreated celiac disease is associated with an increased risk of malignancy, particularly of lymphoma and this relative risk is reduced by the introduction of gluten-free diet. The high prevalence of celiac disease in type I diabetic patients suggests either involvement of the gut in the pathogenesis of type I diabetes or that transglutaminase which is a major auto antigen in celiac disease is a secondary auto antigen resulting from beta- cell destruction.(9)

Early onset of diabetes predisposes to celiac disease and routine serological screening for celiac disease is valuable in type I diabetic patients especially because silent and latent stages of the disease do exist.(10).The prevalence of autoimmune disorders in diabetic patients with celiac disease is higher than in those with type I diabetes alone.(11)Moreover those untreated patients with celiac disease have been found to have a higher than expected prevalence of organ- specific auto antibodies which seem to be gluten- dependent and tend to disappear during gluten - free diet.(12)

Celiac disease is associated with an increased risk of malignancy,(13) and may be complicated by other conditions such as osteoporosis, infertility,(14) and neurologic disorders.(15).Regarding insulin requirements, the mean insulin dose is significantly increased in diabetic patients with positive serology for celiac disease. This finding is related to disturbed metabolic control as evidenced by improved glycemic control in diabetic patients after the diagnosis of celiac disease.(16)

The identification of silent or latent celiac disease with implementation of gluten free diet can prevent the development of symptoms of celiac disease and its complications and possibly the onset of additional autoimmune disorders.(11). Celiac disease is a small intestinal disorder with overt malabsorption in the minority and with sub clinical or atypical symptoms in the majority of patients. It is triggered by gluten and related cereal proteins,(17) the introduction of gluten- free diet will improve the symptoms of celiac disease, growth pattern in children, serum antibody levels, morphology of small intestinal mucosa and control of diabetes mellitus.(18).

In fact, most of the patients with Celiac disease and type I diabetes have few or no symptoms related to malabsorption, and when gastrointestinal complaints are present, they are often mild and appreciated only in retrospect.(19)

The main clinical finding in patients with both celiac disease and diabetes is growth retardation and short stature.(20) Others may present with anemia, weight loss and impaired glycemic control, often with troublesome hypoglycemia which suggests that "brittle diabetes" may be a manifestation of celiac disease.(21).

Material and Method

The present study included thirty children with type I diabetes that were recruited from the regular attendants of pediatric diabetes clinic, king Abdel Aziz hospital, Taif ,KSA. Their ages ranged from 2 to 15 years with a mean of 9.85. Their disease duration (diabetes) ranged from 0.5 – 5 years. With a mean of 1.4 years. All included patients used human intermediate insulin in a dose ranging from 8 – 25.5 I.U/day with a mean of 16.46 I.U/day, also 10 patients were taken as control group; All the patients were subjected to the following: History Taking, Examination, Laboratory investigation: Mean Random blood sugar, Glycosylated hemoglobin (HbA1C), Anti tissue trans glutaminase IgA

Patients and Methods

The present study included thirty children with type I diabetes that were recruited from the regular attendants of pediatric diabetes clinic, king Abdel Aziz hospital, Taif ,KSA. Their ages ranged from 2 to 15 years with a mean of 9.85. Their disease duration (diabetes) ranged from 0.5 – 5 years. With a mean of 1.4 years. All included patients used human intermediate insulin in a dose ranging from 8 – 25.5 I.U/day with a mean of 16.46 I.U/day, also 10 patients were taken as control group;

* All the patients were subjected to the following:

1) History Taking

- Proper, detailed history taking was done with a special concentration on:
- Demographic data: name, age, sex, socio economic class.
- Age at onset of diabetes and disease duration was calculated
- Insulin therapy: regarding type, dose and frequency
- History suggestive acute metabolic complications
- History suggestive hypoglycemic attacks (sweating, headache, blurring of vision, tremors, convulsions, coma)

* History suggestive hyperglycemia (polyuria, polydepsia, polyphagia, loss of weight, coma due to diabetic ketoacidosis.
* History suggestive chronic diabetic complications:
  - Ocular manifestations: persistent blurring of vision flashes of light.
  - Cardiovascular manifestations: palpitation, chest pain, postural hypo tension.
  - Renal manifestations: Polyuria, oliguria, dysuria, loin pain, hematuria.
  - Skin manifestations: Recurrent pyogenic infections, fungal infections.
  - Manifestations of peripheral neuropathy: tingling, numbness, parasthesia, impaired or lost sensations.
  - Gastrointestinal manifestation: dysphasia, hurt burn, anorexia and gastric fullness.
  - Symptoms suggestive celiac disease: abdominal pain, bloating, and recurrent diarrhea (diarrhea was defined as the presence of 3 or more loose stool / day), steatorrhea (if the patient reported large, yellow colored foul smelling, floating stool).
  - Family history of celiac or other auto immune diseases.

2) Examination:

Thorough clinical examination with particular emphasis on:

1- Anthropometric measures: weight in kg and height in cm were plotted against percentiles for age and sex according to the growth charts.
2- Body mass index was calculated by applying the following formula :

$$BMI = \frac{\text{Weight in kg}}{(\text{Height in cm})^2}$$

3- Presence of other autoimmune disorders e.g: vetilligo, alopecia, thyroid swelling and joint abnormalities.
4- Local abdominal examination especially for distention, organomegally or tenderness.

3) Laboratory investigation:

a- Mean Random blood sugar: using glucocard II blood glucose monitoring system, supplied by ARKAY; Inc.
b- Glycosylated hemoglobin (HbA1C): Using quantitive cal metric determination of glyco – HB in the whole blood. Patients were considered to be on optimal glycemic control of HBA1C was <7%, suboptimal it was 7 – 9%, poor if it was > 9%.
c- Anti tissue trans glutaminase IgA:

* Immunomeric enzyme immunoassay for quantitive determination of IgA auto antibodies against tissue transglutaminase.

*** Sample collection and handling:**

3ml of blood were with drowning from the patients through the anticupital vein, using a wide pore needle. Serum of all samples was separated by low speed centrifugation. Only specimens should be used in this procedure. Grossly hemolysed, lypemic or microliably contaminated samples may interfere with the performance of the test, they were excluded serum samples were kept frozen at – 70^{o}c until analysis were performed repeated freezing of the samples was avoided.

*** Principle of the test:**

Human recombinant, tissue transglutaminase is bound to the micro wells antibodies against this antigen, if present in diluted serum of plasma, bind to the respective antigen. Washing of the micro wells removes unspecific serum and plasma components serum antibodies. Horseradish peroxides (HRP) conjugated anti human IgA immunologic ally detect the bound patient antibodies forming a conjugate / antibody / Antigen complex washing of the micro wells removes unbound conjugate an enzyme substrate in the presence of bound conjugate hydrolyses to form a blue colour. The addition of an acid stops the reaction forming a yellow end product. The intensity of this yellow colour

is measured photo metrically at 450 nm. The amount of colour is directly proportional to the concentration of IgA antibodies present in the original sample.

Interpretation of the results:

In a normal range study serum sample from healthy blood donors, the following ranges have been established with the antitissue transglutaminase IgA Antitissue Transglutaminase IgA cut off 10 U/ml.

The values above should be regarded as guidelines only.

d- Antigliadin IgA :

Immunomeric enzyme immunoassay for the quantitive determination of IgA auto anti bodies against gliadin.

* **Sample collection and handling :** As before

* **Principle of the test :** As before

* **Interpretation of the results:**

In a normal study with serum samples from healthy blood donors the following ranges have been established with antigliadin test:

antigliadin Ab IgA normal < 12

(U/ml) elevated ≥ 12

e- Total IgA :

Sample collection and handling : as before

*** Interpretation of the results:**

In a normal range study with serum samples from healthy blood donors the following ranges have been established with the total IgA test.

IgA (Ug/dl) : normal 17 – 94

f- Serum ferritin

Normal range 60 – 160 Ug/dl

Results and Discussion

Table (1): Age, sex distribution, anthropometric measurements of Diabetic cases and Control group

	Cases (N=30)	Control group (N=10)	T	P
Age (Y)				
X ± SD	9.85 ± 2.94	9.4 ± 3.1	0.41	0.68
Range	2 – 15	5 – 13		N.S
Gender	N %	N %		
Male	14 40.0	6 60.0	X2	0.46
Female	18 60.0	4 40.0	0.54	N.S

Weight (kg) X ± SD Range	 32.7 ± 12.8 10 – 59	 34.7 ± 14.7 17 – 58	 0.4	 0.68 N.S
Height (M) X ± SD Range	 1.33 ± 0.1 0.7 – 1.61	 1.32 ± 0.18 0.93– 1.51	 0.03	 0.96 N.S
BMI X ± SD Range	 17.9 ± 3.3 13.87 – 25.53	 18.98 ± 3.9 14.08 – 25.43	 0.85	 0.59 N.S

Table (1) Compares the age, Gender between group I (30 diabetic children), group II (10 healthy children), there was no statistically significant difference, a result confirming that the sample was homogenous.And Compares the anthropometric measurements between the above mentioned the 2 groups.

Table (2) Laboratory investigations including (RBS, HBA1C, anti TTgIg A, antigliadin IgA, IgA) which were done to diabetic cases and control group

	Cases (N=30)	Control group N=10	K	P
RBS (mg/dl) X ± SD Range Median	 261.9 ± 126.6 55 – 550 237	 96.7±21.7 70-135 90	 13.58	 0.001 H.S
HBA1C (%) X± SD Range Median	 7.9 ± 1.03 5.9 – 10 8.05	 5.26 ± 0.6 4.5 – 6 5.3	 T 7.7	 0.001 H.S
Anti TTG IgA (U/L) X ± SD Range Median	 5.24 ± 4.86 0.2 – 17 3.05	 0.48 ± 0.3 0.1 – 1.0 0.45	 19.83	 0.001 H.S
Total IgA (Ug/dl) X ± SD Range Median	 181.7 ± 208.4 19 – 800 90.5	 43.4 ± 19.5 19 – 80 60	 8.175	 0.004 Sig.

Antigliadin IgA (U/L)				
X ± SD	6.8 ± 6.4	0.78 ± 0.28	18.7	0.001
Range	0.9 – 21.1	0.3 – 1.2		H.S
Median	4.2	0.8		

Table (2) Compares the investigations dons to the above mentioned 2 groups; as Regarding Random Blood sugar, we found a highly significant difference (p=0.001) between diabetics and control group as the mean RBS in diabetics was 261.9 mg/dl while it was 96.7 mg/dl in control group.

As Regards the metabolic control, we found highly significant difference (P=0.001) between diabetics and control group as the mean HBA1C in diabetics was 7.9% while it was 5.28 % in control group.

As Regards the antitissuetransglutaminase IgA, we found a significant difference (P=0.001) between diabetics and control group as the mean TTgIgA in diabetics was 5.24 U/ml while it was 0.48 U/ml in control group.

Studying the levels of antigliadin IgA, we found a significant difference (P = 0.001) between diabetics and control group as the mean antigliadin IgA in diabetics was 6.8 U/ml while it was 0.78 U/ml in control group.

As Regards IgA, we found a significant difference (P=0.004) between diabetics and control group as the mean IgA in diabetics was 181.7 Ug/dl it was 43.4 Ug/dl in control group.

Table (3) Includes the serological prevalence of CD in the studied negative cases with no statistically significant difference (P=0.54).

Table (3): The prevalence of celiac disease in diabetic cases and control group according to different serological tests

	Cases		Control group		X2	P
	N	%	N	%		
TTgIgA (U/l)						
Negative	26	86.7	10	100.0	0.37	0.54
Positive	4	13.3	0	0.0		N.S
Antigliadin IgA (U/l)						
Negative	22	73.3	10	100.0	5.27	0.17
Positive	8	26.7	0	0.0		N.S
IgA (Ug/dl)						
Negative	16	53.3	10	100.0	5.27	0.02
Positive	14	46.7	0	0.0		Sig

As regards the antigliadin IgA, there were 8 positive, 22 negative cases, with no significant difference (P=0.17)

As Regards IgA, there were 14 positive, 16 negative cases with a significant difference (P=0.02).

Table (4): Serum ferritin in diabetic cases and control group

	Cases (N=30)	Control group (N=10)	T	P
S. Ferritin (Ug/dl)				
X ± SD	176.93 ± 60.04	135.9 ± 27.58	2.07	0.04
Range	105 – 310	104-202		Sig

Table (4) Compares serum ferritin between the above mentioned 2 groups, we found a significant difference (P=0.04) between diabetics and control group as the mean S. ferrtin in diabetics was 176.93 Ug/dl while it was 135.9 Ug/dl. In control group.

Results

As regards the sex distribution in our patients, we found that CD had more common occurrence in female, although the difference in sex distribution with non celiac diabetic patients was non significant. As Regarding Random Blood sugar, we found a highly significant difference (p=0.001) between diabetics and control group as the mean RBS in diabetics was 261.9 mg/dl while it was 96.7 mg/dl in control group. As Regards the metabolic control, we found highly significant difference (P=0.001) between diabetics and control group as the mean HBA1C in diabetics was 7.9% while it was 5.28 % in control group. As Regards the antitissuetransglutaminase IgA, we found a significant difference (P=0.001) between diabetics and control group as the mean TTgIgA in diabetics was 5.24 U/ml while it was 0.48 U/ml in control group. Studying the levels of antigliadin IgA, we found a significant difference (P = 0.001) between diabetics and control group as the mean antigliadin IgA in diabetics was 6.8 U/ml while it was 0.78 U/ml in control group. As Regards IgA, we found a significant difference (P=0.004) between diabetics and control group as the mean IgA in diabetics was 181.7 Ug/dl it was 43.4 Ug/dl in control group. As regards the antigliadin IgA, there were 8 positive, 22 negative cases, with no significant difference (P=0.17). As Regards IgA, there were 14 positive, 16 negative cases with a significant difference (P=0.02). As Regards we found a significant difference (P=0.04) between diabetics and control group as the mean S. ferrtin in diabetics was 176.93 Ug/dl while it was 135.9 Ug/dl in control group

Conclusion

From this study we can entail that; the prevalence of biopsy - proven celiac disease in our type 1 diabetic patients was 10%. Most of those patients were presented in an atypical or silent form. Therefore a serological screening anti TTgIgA testing was required for early detection. This test had a sensitivity and specificity 100% and 95% respectively in our study.

Hence, we can conclude the following findings: Serological screening of IDDM children allowed us to detect precociously associated Celiac disease, evaluate the true prevalence of Celiac disease in those patients and to start the specific diet.

Celiac disease is sufficiently prevalent in type 1 diabetic patients and that the benefits of the diagnosis and treatment were enough, that this disorder should be actively sought in all IDDM patients.

Celiac disease in type 1 diabetic patients had significantly affected the degree of glycemic control.

Anti TTgIgA positivity was not related to age or sex of the diabetic patients yet it was related to the disease duration of the affected patients.

Celiac disease in diabetic patients had no effect on the occurrence of acute diabetic complications i.e. DKA and hypoglycemia.

Finally, in this study we want not only to focus on the avoidance of acute problems of IDDM but also on long - term results, and substantial progress which had been achieved regarding the guidance of those patients. Basically, the situation in CD is very similar to that in DM. Pediatricians have to focus not only on the patients present well-being but also on maintaining their health on the long term.

Recommendations

(1) Celiac disease should be brought in mind in type 1 diabetic patients with any constitutional symptom whatever its severity.

(2) The regular work up of diabetic patients should include serological screening for CD, because a delay in detection of associated CD may lead to clinically relevant, but otherwise preventable complications.

(3) We recommend to use anti TTgIgA as a screening for CD in type 1 diabetic patients not only because of its high sensitivity and specificity but also because it is highly correlated with the mucosal changes in the biopsy finding.

(4) Upper GI endoscopy and intestinal biopsy should be mandatory to confirm CD diagnosis.

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