CLINICAL SPECTRUM OF COMORBID COELIAC DISEASE IN TYPE 1 DIABETES MELLITUS- A TERTIARY CARE CENTRE BASED STUDY IN ASSAM MEDICAL COLLEGE AND HOSPITAL

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ABSTRACT

BACKGROUND

The relationship between T1DM and CD has been known due to their identical genetic and autoimmune background. The prevalence of CD in T1DM in Assam has not been determined. We examined the prevalence and clinical profile of CD in patient with T1DM in Assam.

MATERIALS AND METHODS

A cross-sectional study with 96 patients with T1DM from the Outpatient or Inpatient Department of Medicine of Assam Medical College and Hospital, Dibrugarh, was undertaken in the study period from July 1, 2015, to June 30, 2016. Anti-Tissue Transglutaminase Antibody (anti-TTG) measurement was done by ELISA in all patients. Duodenal biopsy were performed for T1DM patients with positive and negative serology for anti-TTG antibodies.

RESULTS

Total 96 T1DM patients (51 males and 45 females) with the age ranging from 12-50 years (mean ± SD 24.24 ± 6.89) were studied. Elevated anti-TTG levels were found in the sera of 4 (4.17%) out of 96. The male-to-female ratio of the anti-TTG positive is 1:1. Serology positive patients had typical symptoms along with statistically significant association of neuropathy, anaemia, hypoalbuminaemia and hypocalcaemia. Duodenal mucosal biopsy of one IgA tTG positive patient was Marsh3a type. Out of 12 T1DM who were serology negative for CD, 1 had Marsh type 3a, 2 had type 2, 5 had type 1 and 4 had type 0 (normal).

CONCLUSION

Celiac disease in T1DM is not uncommon in this part and prevalence is 4.17%. Suspected cases needs evaluation by serological test along with histopathological examination of duodenal mucosa. Serum IgA measurement and genetic study can be considered in serology-negative patients with typical symptoms of celiac disease.

KEYWORDS

Celiac Disease, Type 1 Diabetes Mellitus, Clinical Spectrum.

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BACKGROUND

CD is a chronic, multiple-organ autoimmune disease that primarily affects the small intestine in genetically predisposed individuals. It is precipitated by dietary gluten and related prolamin present in wheat, barley and rye.[1] It usually presents with protean of clinical symptoms of malabsorption such as chronic diarrhoea, weight loss, steatorrhoea, hypoalbuminaemia, nutritional anaemia and several extraintestinal manifestations involving skin, thyroid, pancreas, heart, liver, joints, muscles, bones, reproductive system, as well as central and peripheral nervous systems in all age groups.[2] The prevalence and disease severity is more in females in comparison to male. Though small intestinal biopsy is considered gold standard for diagnosis of CD, with the advent of highly sensitive and specific serological test, it has become easier to screen high-risk population. The prevalence of CD in patients with T1DM is approximately twenty fold higher than that of general population and ranges from 3 to 16%.[3,4,5] It is around 4.5% of children and almost 6% of adults with T1DM. The concurrence of the two diseases maybe explained by identical genetic background associated with HLA DQ2 and DQ8 and similar trigger mechanism for autoimmune process. HLA class II molecule located in short arm of chromosome 6 DQ8 (DQB1*0302-DQA1*0301) and DQ2 (DQB1*0201-DQA1*0501) have been

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identified as key genetic risk factors in both CD and T1DM.[6] DQ8 conveys a higher risk factors for T1DM, where DQ2 is more frequently associated with CD.[7] There is positive correlation of occurrence of celiac disease with the advancing age and duration of type 1 diabetes.[8]

Out of the estimated 422 million diabetic population in 2016, globally 5 to 10% accounts for T1DM and 23% of the T1DM belongs to South East Asia.[9,10,11] But, the studies regarding the comorbidity of CD in T1DM is limited. In a recent study by Ramakrishna BS et al found that large proportion of people of Assam use wheat as their staple food and are also genetically predisposed to celiac disease.[12] Considering the above facts, this study has been undertaken with the following objective to evaluate the association of CD and its clinical profile among the T1DM.

MATERIALS AND METHODS

The present study was carried out on T1DM patients who attended the outpatient department and/or were admitted in the various units of Department of Medicine, Assam Medical College and Hospital, Dibrugarh.

Study Design- Hospital-based observational study done from July 1, 2015, to June 30, 2016.

Ethical Considerations- Ethical clearance was obtained from the Institutional Ethics Committee prior to the onset of study.

Sample Size- All the old and newly-diagnosed patients of T1DM.

Inclusion Criteria

All the old and newly-diagnosed cases of T1DM were included in this study.

Exclusion Criteria

1. Age less than 12 years.
2. Patients not giving consent.

Methodology- All clinically suspected type 1 DM cases attending Medicine OPD or admitted as inpatients in AMCH Dibrugarh, fulfilling inclusion and exclusion criteria were included in the study. A total of 96 such patients were available. Written informed consent from the patients/guardian was taken prior to enrolling in the study. A detailed clinical history, physical examination and relevant investigations were done in all the patients and filled in a predesigned proforma. All the 96 type 1 DM patients were then evaluated for CD by doing ELISA test for IgA anti-TTG antibody in the serum. Out of 96 T1DM patients, 4 came out to be positive. One of the IgA anti-TTG positive patient gave consent and was subjected to duodenal biopsy, which confirmed the presence of CD. Another 12 patients also underwent duodenal biopsy and 8 patients had mucosal changes, which were staged according to Marsh histopathological staging for CD.

Case Definitions[13]

Type 1 diabetes mellitus will be diagnosed on clinical ground in adults presenting with hyperglycaemia (random blood glucose ≥200 mg/dL or 11.1 mmol/L) with typical presence (but not always) of one or more of the followings-

- Ketosis.
- Rapid weight loss.
- Age of onset below 50 years.
- BMI below 25 kg/m2.
- Personal and/or family history of autoimmune disease.

Statistical Evaluation

All the categorical variables were expressed as percentages and all continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using Fisher's exact test and Chi-square test, whichever is applicable. Continuous variables were compared using independent t-test and ANOVA as applicable. P values <0.05 were taken as significant. Pearson's correlation coefficient is used to calculate bivariate correlations. Statistical analysis was performed by using software SPSS version 17.

RESULTS

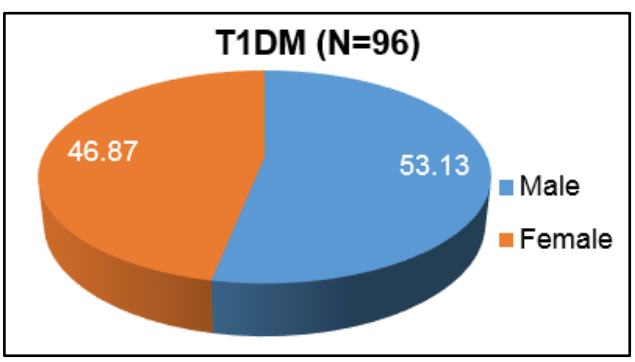

Figure 1. Male and Female Distribution of T1DM

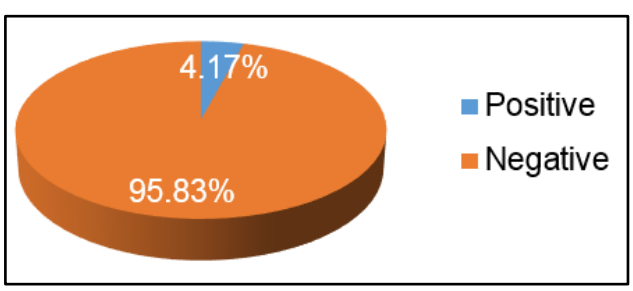

Figure 2. Serum IgA Anti-TTG Antibody in 96 T1DM Patients

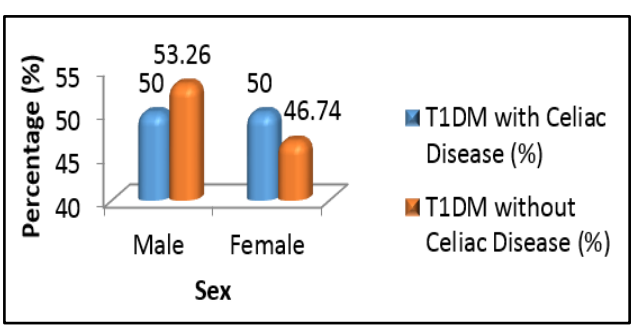

Figure 3. Gender Distribution

	T1DM With Celiac Disease		T1DM Without Celiac Disease		P Value
	Mean	SD	Mean	SD	
Age (years)	24.75	4.86	24.22	6.99	0.881
Duration of diabetes (months)	40.5	60.04	37.07	54.78	0.903
Height (cm)	154.25	3.86	159	8.99	0.297
Weight (kg)	40	3.56	44.84	8.98	0.288
BMI (kg/m^2)	15.84	1.09	17.71	2.74	0.179
RBS (mg/dL)	670.00	134.12	567.55	152.91	0.19
FBS (mg/dL)	264.50	103.90	283.96	123.08	0.75
PPBS (mg/dL)	378.75	174.06	359.12	139.88	0.78
HbA1c%	11.98	2.85	10.66	3.03	0.395

Table 1. Anthropometry and Glycaemic Status of the Patient of T1DM With and Without CD

	T1DM With CD		T1DM Without CD		P Value
	Numbers	Percentage	Numbers	Percentage	
Chronic/recurrent diarrhoea	3	75	40	43.48	0.322
Recurrent blood in stool	1	25	12	13.04	0.447
Recurrent abdominal pain/distension	2	50	41	44.57	1
Chronic/recurrent constipation	2	50	33	35.87	0.621
Recurrent vomiting	1	25	12	13.04	0.447
Recurrent hypoglycaemia	2	50	46	50	1
Oedema	2	50	10	10.87	0.075
Mouth ulceration	2	50	16	17.39	0.158
Dental enamel defect	1	25	11	11.96	0.419
Neuropathy	3	75	17	18.48	0.027
Retinopathy	1	25	12	13.43	0.447
Nephropathy	1	25	13	14.13	0.473
Diabetic foot	0	0	3	3.26	1
Cataract	0	0	3	3.26	1
Hypothyroidism	0	0	10	10.87	1
Other autoimmune disease	0	0	2	2.17	1
Septicaemia	2	50	30	32.61	0.599
Osmotic symptoms	4	100	76	82.61	1
DKA	3	75	55	59.78	1
Tuberculosis	0	0	2	2.17	1

Table 2. Distribution Celiac-Related Symptoms and Comorbid Disease in T1DM Patients With and Without CD

Laboratory Parameters	T1DM With Celiac Disease (N=4)		T1DM Without Celiac Disease (N=92)		Total = 96		P Value
	No	%	No	%	No	%	
Anaemia (Hb% <11 g/dL)	4	100	38	41.3	42	43.75	0.034
Hypoalbuminaemia (albumin <3.4 g/dL)	4	100	40	43.48	44	45.83	0.041
Elevated AST (>37 U/L)	3	75	38	41.3	41	42.71	0.309
Elevated ALT (>78 U/L)	3	75	25	27.2	28	29.17	0.073
Elevated ALP(>116U/L)	3	75	33	35.87	36	37.5	0.147
Hypocalcaemia (<8.5 mg/dL)	3	75	14	15.22	17	17.71	0.017
Low C peptide (<0.5 ng/mL)	3	75	67	72.83	70	72.92	1

Table 3. Other Laboratory Parameters

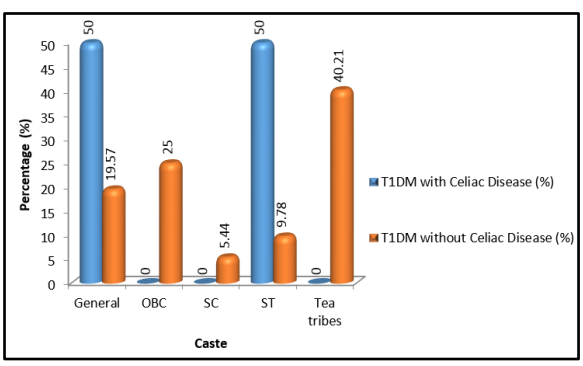

Figure 4. Caste Wise Distribution

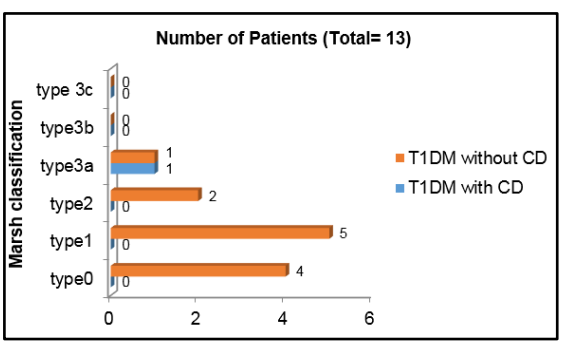

Figure 5. Histological Findings of Duodenal Mucosa in Patients with Type 1 DM With and Without CD

CONCLUSION

In the study, out of 96 T1DM patients, 53.13% were male and 46.87% were female (M:F = 1.13:1). This male and female distribution of T1DM almost coincides with the data according to the phase I (2006-2011) report of the 10 collaborating center of Registry of People with Diabetes in India with young age at onset under ICMR in 51.8% of T1DM is male and 48.2% is female.

The prevalence of IgA anti-tTG positive CD in this studied population is 4.17%. Elfstorm P. et al[14] in a large meta-analysis found that the prevalence of CD in T1DM ranges from 1.6% to 12.3%.

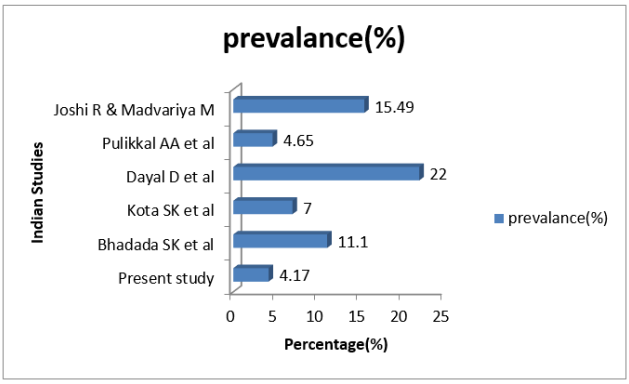

Figure 6. Prevalence of CD in T1DM in Different Studies in India

The difference in genetic and food habits maybe the cause of low prevalence of CD in this region in comparison to North Indian T1DM patients.

The age distribution of CD with T1DM is 24.75 ± 4.86 years, while that of T1DM patients without CD is 24.22 ± 6.99 years. In a study in Southern Kerala by Jacob A and Kumar S (2008) found that the age distribution was 15 ± 5.54 years (mean ± SD) in T1DM with CD in comparison to 22.42 ± 8.88 years in T1DM without CD (186). Bhadada S.K. et al found the mean age of the 21 CD patients with T1DM was 13.74 ± 5.71 years.

The male-to-female ratio of CD is found to be 1:1 in this study. Pham-Short et al,[15] Glastras S.J. et al,[16] Annie A et al got equal male-to-female ratio. But, the ratio is different in different studies.

38.54% of T1DM were from tea tribes. But, IgA anti-tTG positive patient was not found in this community. Out of the 4 CD patients, 2 were from general community, which constitute 20.83% and 2 were from tribal community contributing only 11.46% of total T1DM patients. Possibly, the genetic makeup of tea tribes maybe different that protects them from CD predisposition. So, genetic study is necessary to establish this fact. Difference in food habits, cultural practices (e.g. breastfeeding) and role of other environmental factors also need evaluation.

The mean duration of T1DM for the four CD patients is 40.5 ± 60.04 months and 3 (75%) were diagnosed within 6 months of diagnosis of T1DM. In the meta-analysis by Pham-Short et al, out of 587 biopsy-proven CD in 11,157 T1DM patients, 40% were diagnosed within one year, 55% within 2 years and 79% were diagnosed within 5 years of diagnosis of diabetes. Alshareef A.M. et al in their study found that 31.25% of CD patients were diagnosed within 12 months of diagnosis of T1DM. In the studies by Bhadada et al and Pulikkal A A et al found that the lag period between diagnosis of T1DM and CD was 5.18 ± 4.75 years and 8.8 ± 4.64 years, respectively. An earlier age at onset of diabetes was predictive for positive celiac antibodies. The chance of co-morbidity of CD increases with duration of diabetes. In this study, the diagnosis of 3 CD within 12 months of T1DM can be explained by the fact that CD may have preceded diabetes.

All the 4 patients in the study had osmotic symptoms and 3 (75%) had history of DKA. On the other hand, 59.78% T1DM patients without CD had history of DKA. In the study by Jacob A. and Kumar S., DKA was found in 1 (14.29%) out of 7 CD patients with T1DM in comparison to 26 out of 63 T1DM without CD (41.27%).

Three (75%) of the CD patients had chronic diarrhoea, 2 had history of recurrent abdominal pain, recurrent hypoglycaemia, oedema and oral ulcer and 1 had dental enamel defect. Bashiri et al in their study found that 20% of T1DM patients with CD had diarrhoea, 30% had abdominal distension, 25% had oral ulcer and oedema was present in 15%. In the study by Bhadada SK et al, diarrhoea was present in 28.6%, abdominal pain in 14.3%, whereas 23.8% of CD with T1DM were asymptomatic. In the meta-analysis of Pham-Short et al, 85% of CD patient in T1DM are asymptomatic. Routine stool examination with measurement of total fat content is necessary to differentiate CD from autonomic gastropathy in T1DM with recurrent gastrointestinal symptoms. Mohan et al in a study found that CD patients with T1DM patients had more frequent hypoglycaemia in comparison to control due to malabsorption. So, T1DM patient presenting with recurrent hypoglycaemia, CD should be ruled out.

In this study, no significant difference is observed in terms of height and weight in T1DM patients with and without CD. Pulikkal A et al in their study also did not find any significant difference in height and weight between IgA anti-tTG positive and negative T1DM patients.[17] Kaspers S. et al in a cohort study in 19,796 paediatric patients with T1D found that the CD-affected patients were significantly younger at diabetes onset and had significantly lower height and BMI. Evidence for thyroid disease was more commonly observed in the T1D with CD group and HbA1c values were lower in the patients with T1D and CD. Frohlich-Reiterer EE et al also found that patients with biopsy-proven celiac disease had a significantly lower weight and height compared with patients without CD. So, screening for celiac disease is important in T1DM patients to prevent persistent growth failure. In this study, this mean age of T1DM with IgA-tTG antibody positive CD is 24.75 ± 4.86 years and duration was 40.5 ± 60.04 months. While IgA anti-TTG antibody negative T1DM patients has mean age is 24.22 ± 6.99 years and duration is 37.07 ± 54.78 months. It indicates that most of the patients were diagnosed after epiphyseal fusion of long bones. This maybe a cause of insignificant height and weight difference between CD

positive and negative groups. In this study, all the 4 CD with T1DM patients were underweight in comparison to 51% of T1DM without CD.

3 IgA-tTG serology positive patients had peripheral neuropathy (75%). There is significant association of neuropathy in celiac disease patient in comparison to T1DM without CD group. Leeds J. S. et al in a study found peripheral neuropathy in 41.6% (5/12) of celiac disease with T1DM. Cicarelli G. et al in a study found that 50% of celiac disease patient may develop peripheral neuropathy due to nutritional deficiency. So, a T1DM patient with early presentation of neuropathy, CD should be kept in consideration. One T1DM patient with CD had nonproliferative diabetic retinopathy. The duration of diabetes in this case is 12 years. In a study by Mollazadegan K et al concluded that having a diagnosis of CD for >10 years is a risk factor for the development of DRP in T1D and merits intense monitoring. Bakker SF et al in their study found that T1DM with CD patients have less retinopathy in comparison to those without CD.[18] The patient with retinopathy had stage 2 nephropathy. Pham-Short et al found that concomitant CD in T1DM patients increases the risk of nephropathy.

In this study, 2 CD (50%) patients had septicaemia in comparison to 32.61% of T1DM patients without CD. But, whether association of CD in T1DM patients increases risk of septicaemia or not needs long prospective study.

10.87% of T1DM patients without CD had hypothyroidism. On the other hand, out of 4 CD patient, one had subclinical hypothyroidism with TSH level 7.23 mU/L. Bhadada SK et al found hypothyroidism in 14.3% out of 21 T1DM patients with CD. Joshi R. and Madvariya M in their study detected autoimmune thyroiditis in 54.5% among the CD group and 25% among the non-CD group. While hypothyroidism was found in 36.3% among CD group in comparison to 5% of non-CD group. Thus, AITD was the most common autoimmune disease found in this cohort of T1DM patients. Overall, the prevalence of overt hypothyroidism was 8.4%, while that of subclinical hypothyroidism was 11.26%. Other studies also found that patients with CD had an increased risk of thyroid autoimmune disorders.

In this study, no significant association of CD with glycaemic status is found. Frohlich-Reiterer EE et al in a large cohort found no statistically significant differences in mean HbA1c levels, between children with and without CD after 5 years of follow-up.

All the 4 patients had microcytic hypochromic anaemia and hypoalbuminaemia, while 3 patients had hypocalcaemia. These parameters had significant 'p' value <0.05. Joshi R. and Madvariya M in their study found anaemia in 54.5% CD patient in comparison to 20% T1DM without CD. Hypocalcaemia was found in 9% of CD patients with T1DM. These findings had significant 'p' value. Tursi A et al in a study found IDA in 27.77%, osteoporosis in 6.81% of CD patients.[19] So, nutritional supplement with calcium, iron vitamin B12 as well as folic acid supplementation is necessary along with other micronutrients with diagnosis of CD in T1DM patients.

The level of C-peptide level of T1DM patients with CD was 0.485 ± 0.39 ng/mL, while it was 0.473 ± 0.589 in T1DM without celiac disease group. But, no significant association was found between the two groups of T1DM patients with and without CD.

13 T1DM patients had undergone duodenal biopsy. Only one IgA anti-tTG positive patient gave consent for duodenal biopsy and duodenal mucosal change is Marsh type 3a. Out of the rest 12 T1DM patients who were IgA anti-tTG negative, one had type 3a, two had type 2, five had type 1 and 4 had type 0 duodenal mucosal finding according to Marsh modified (Oberhuber) classification. Rahmati A et al in a study in 159 CD patients found that the duodenal mucosal damage is related to IgA anti-tTG titers. They suggest that duodenal biopsy is not always necessary for diagnosing CD and when tTG level is more than 9 folds higher than the cut-off value.[20] Rubio-Tapia A et al in their guideline for CD says that IgA deficiency is more common in CD patients than general population.[21] So, measurement of IgA level can be considered in IgA anti-TTG negative patients with high clinical suspicion. In case of low IgA level, we have to go for IgG based serological tests. They also recommends that if the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative.

HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out celiac disease in selected clinical situations like equivocal small bowel histological finding (Marsh I-II) in seronegative patients, evaluation of patients on a GFD in whom no testing for CD was done before GFD. Patients with discrepant celiac-specific serology and histology after ruling out other causes of lymphocytic duodenosis and villous atrophy.

Hence, co-occurrence of both these conditions influence the quality of life as treatments are burdensome and complications can be debilitating and life-threatening. Though the prevalence of CD in northeastern region is lower in comparison to North Indian population, however, it is most often overlooked and growing like iceberg phenomenon. Early diagnosis and initiation of GFD under regular supervision may prevent further deterioration of T1DM with CD, which like the iceberg threatens to grow bigger.

Limitations of the Study

This study had limitations in terms of a smaller sample size, lack of control group. Though in this study, highly sensitive (95.7%) and specific (98%) IgA anti-tTG ELISA kit was used, but estimation of serum IgA level was not done in negative cases. Besides duodenal mucosal biopsy could be done only in 13 patients, so the underestimation of prevalence cannot be denied.

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