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Research Article

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Screening Diabetic Children and Adolescents for Asymptomatic Coeliac Disease: Is It Beneficial? Tripoli University Hospital, Tripoli-Libya

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ABSTRACT

Coeliac disease (CD) is common in children and adolescents with type 1 diabetes mellitus; and hence CD screening of all asymptomatic diabetic children is conducted in many countries. While introduction of a gluten-free diet (GFD) might improve glycaemic control, the burden of two dietary regimes is a great challenge for the patient, the caretakers, and healthcare professionals.

The study was aimed to assess the short-term effects of the diagnosis and treatment of asymptomatic CD in children and adolescents with type 1 diabetes on their diabetic control and body mass index (BMI), one year before and two years after diagnosing CD and introducing GFD in Tripoli University Hospital, Tripoli, Libya.

Observational longitudinal case-control study of 26 diabetic children with CD and 26 diabetic children without CD as controls, matched for age, sex, and duration of diabetes.

The age at diagnosis of diabetes mellitus in coeliac group and controls was 6.0 ± 3.98 years and 5.8 ± 3.86 years, respectively (P = 0.8). The coeliac cases were diagnosed with CD at 10.3 ± 4.27 years of age. HbA1c levels were 9.76% ± 2.49%, 9.54% ± 2.77%, and 9.62% ± 2.64% in controls, coeliac cases pre-GFD, and post-GFD, respectively. HbA1c did not change in coeliac cases 1 year before and 2 years after introduction of GFD, but insulin requirements and BMI SDS increased significantly. HbA1c values during pre-GFD and after-GFD periods were similar to those of controls with the exception of insulin requirement, which was significantly higher after diagnosis of CD than in controls (1.01 ± 0.27 unit/kg/day vs. 0.94 ± 0.25 unit/kg/day, P = 0.009), and BMI in control group was higher than those of both periods in celiac group. Individual analysis of all values at each time point between cases and controls did not reach statistical significance over the two-year period.

This study suggests that diagnosing CD and introducing GFD in diabetic children have no effect on glycaemic control. However, it is associated with an increase in daily insulin requirements.

Key words- *Coeliac disease; Type 1 diabetes, Gluten-free diet.*

INTRODUCTION

Coeliac disease (CD) can be asymptomatic.[1] The only known treatment of CD is lifelong gluten-free diet (GFD)[2] which involves excluding wheat, barley, and oats.[3] Type 1 diabetes mellitus and CD share the same HLA loci namely A1, B8, DR3, and DQ2.[4] Moreover, there are suggestions that altered intestinal permeability in genetically susceptible subjects would induce an autoimmune reaction against β-cells in the pancreas in young children.[5]

The risk of developing CD in diabetic child is negatively and independently associated with the age of onset of diabetes mellitus. Thus, children aged less than 4 years have a threefold risk (odds ratio = 3.27) compared with those aged over 9 years. Moreover, girls are more susceptible to develop both CD (with odds ratio of 1.93) and diabetes.[5] Sadly, elimination of dietary gluten protein in non-diabetic children with positive autoantibodies has not shown a protective effect in preventing diabetes or in altering autoanitbodies levels in high risk individuals with a positive family history of diabetes mellitus .[6]

Screening policy differs from country to another and changes overtime[7-12] Screening for asymptomatic CD in type 1 diabetes has created a dilemma among paediatricians. In children with CD and type 1 diabetes, several studies reported that less than 30% of patients were strictly compliant with a GFD .[13] The natural history of undiagnosed asymptomatic CD is also unclear. Additionally, the long-term complications of CD are recognised in clinically diagnosed symptomatic patients and not in those detected by screening.[2] Even the use of multiple terminologies for diabetic patients with CD in literature (silent, potential, latent, subclinical, mild, screening-identified CD) reflects the uncertainty and limited information about the natural history, pathogenesis and modifying factors of CD.[14] It is difficult for children and their

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families to strictly comply with GFD, and remain motivated to do so, when they notice few if any ill effects when a normal diet is consumed.[3] Arguably, screening could compromise glycaemic control due to poor dietary compliance, leading to development of troublesome diabetic complications such as nephropathy, retinopathy, and neuropathy even during childhood. The quality of life may also deteriorate because of the newly diagnosed disease involving a restrictive diet adding more stress and anxiety to the child and the family. This new diagnosis may enhance psychological stress in diabetic children and adolescents because they need more attention to their diet and it may restrict their participation in many common activities with peers.[1]

Many case-control and observational studies have shown different results concerning the impact of CD screening and its treatment on glycaemic control in children with type 1 diabetes.[15] This could reflect the effect of small sample size, lack of controls in some studies, cross-sectional design in few of them, varied or poor dietary compliance, and selection bias arising from choosing clinic- based cohorts instead of population-based cohorts.[15] For this reason, there is still a need to investigate the effect of CD screening and treatment on glycaemic control in children with type1 diabetes in different settings with more subjects and more controls.

The aim of our study is to evaluate the effect of the diagnosis and treatment of asymptomatic CD on glycaemic control in children with type 1 diabetes mellitus in a large paediatric centre.

MATERIALS AND METHODS

This longitudinal, clinic-based matched comparative study evaluated the diabetic control one year before and two years after CD diagnosis and introduction of GFD in children with type 1 diabetes diagnosed during 1997-2012 in Paediatric Endocrine Clinic in Tripoli University Hospital (TUH), Tripoli, Libya.

The screening policy for CD in children with type 1 diabetes in TUH involves testing at the time of diagnosis of type 1 diabetes, followed by screening every 2-3 years thereafter. After a positive anti-tissue transglutaminase (tTG) or anti-endomysial (EMA) antibody results, then the diagnosis of CD is confirmed by pathological examination of jejunal biopsy.

The inclusion criteria for coeliac cases were: all children with type 1 diabetes, developed CD after a minimum of 1 year of the diagnosis of diabetes. Inclusion criteria for control subjects were: children with type 1 diabetes with no history of CD. Exclusion criteria for both groups were: patients on insulin pump therapy, Down syndrome, symptomatic CD, any other chronic medical condition require lifelong treatment such as hypothyroidism.

Twenty-six diabetic subjects with CD (13 boys and 13 girls) were identified and matched with 26 diabetic controls from the same clinic according to gender, age, and duration of diabetes. Information was collected regarding: glycosylated haemoglobin A1 (HbA1c), body mass index (BMI) (kg/m^2), mean insulin dose (unit/kg/day). BMI were converted to standard deviation scores (SDS) using QuesGen software (Pediatric Percentile Calculator)[16] with Centers for Disease Control and Prevention (CDC) reference data for BMI.[17] The project was approved by the head of department of pediatric endocrinology at TUH.

RESULTS

The study and control groups consisted of 26 patients each, with 13 girls in each group. The age at diagnosis of diabetes mellitus in the coeliac group and controls was 6.0 ± 3.98 years and 5.8 ± 3.86 years, respectively (P =0.8). The coeliac cases were diagnosed with CD at 10.3 ± 4.27 years of age, after 4.3 ± 2.77 years of type 1 diabetes (Table 1).

HbA1c

In the year before diagnosis of CD, the mean HbA1c of coeliac cases was 9.54% ± 2.77%. In the following two years, the mean had increased to 9.62% ± 2.64%. However, it did not reach statistical significance. In the control group, the mean HbA1c was 9.76% ± 2.49%, and was similar to coeliac cases when compared with HbA1c of cases in both periods (P = 0.856) (Table 2). When comparing HbA1c in the controls and the coeliac cases at each time point. HbA1c was similar in all time points.

Daily Insulin requirements

The daily insulin requirement in coeliac cases prior to introducing GFD was 0.89 ± 0.27 unit/kg/day. In the following two years, it increased significantly to 1.01 ± 0.27unit/kg/day (P = 0.003). On the other hand, the insulin requirement in control group was 0.94 ± 0.25 unit/kg/day. This dose was similar to insulin dose during pre-CD period in cases, and it was significantly lower than the insulin dose after diagnosis of CD (P = 0.009) (Table 2). Insulin requirements of the control group were generally lower than that of coeliac case at most time points (Figure 1). Despite this difference, individual analysis of each time point did not show any statistical difference, the graph showed increasing trend in insulin doses in cases especially after the diagnosis of CD.

BMI

BMI SDS increased significantly from 0.02 ± 0.88 to 0.13 ± 0.79 in the period before and after the diagnosis of CD respectively (P = 0.003). In the control group, BMI SDS was 0.45 ± 0.93 which was higher than both periods of CD case (P <0.001) (Table 2).

Table 1: Comparison of demographic characteristics between diabetic children with CD and diabetic matched controls.

	Coeliac cases	Control subjects	*P*-value
Number (females)	26 (13)	26 (13)	
Age at diagnosis of diabetes (years)	6.0 ± 3.98 [2 – 13.9]	5.8 ± 3.86 [1.5 – 14.1]	0.8
Age at diagnosis of CD (years)	10.3 ± 4.27 [3.8 - 16.7]	-	

Table 2: Comparison of glycaemic control and BMI between diabetic children with CD (1 year before and 2 years after the introduction of GFD) and diabetic matched controls.

Variables	Control subjects	Subjects with CD (before GFD)	Subjects with CD (after GFD)
HbA1c (%)	9.76 ± 2.49 [4.4-17.6]	9.54 ± 2.77 [4.8-15.5]	9.62 ± 2.64 [4.7-14.8]
Insulin requirements (units/kg/day)	0.94 ± 0.25 [0.41-1.91]	0.89 ± 0.27 [0.34-1.65]	1.01 ± 0.27* [0.42-1.83]
BMI SDS	0.45 ± 0.93 [-3.66 – 3.4]	0.02 ± 0.88* [-2.09 – 1.74]	0.13 ± 0.79* [-2.24 – 1.91]

*P <0.05 vs. Control subjects.

In specific analysis at each time point, BMI SDS readings in control group were higher than that of cases' although they did not reach statistical significance except the 6-month time point prior to CD diagnosis ($P = 0.01$).

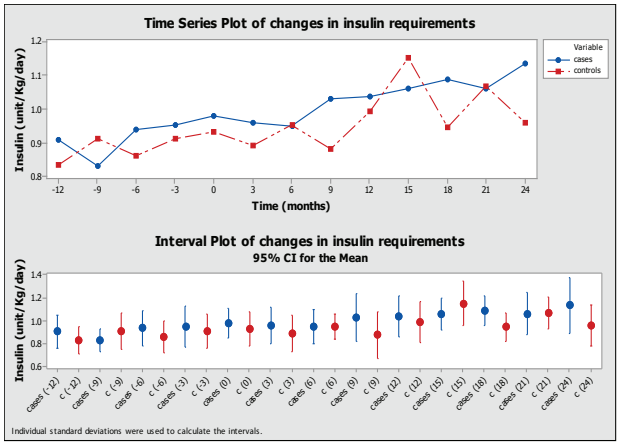

Figure 1: Daily insulin requirements in coeliac and control groups plotted against time relative to diagnosis of CD and introduction of GFD (cases for coeliac case and c for controls).

DISCUSSION

Our study showed no significant difference in glycaemic control one year before diagnosing CD and two years post introduction of GFD in diabetic children with asymptomatic coeliac disease, when compared with matched controls. However, the daily insulin requirements have increased after the introduction of GFD in the CD group, compared with both pre-CD diagnosis and controls. BMI increased after introducing GFD in CD cases, but BMI measurements in controls were higher than CD cases over the 3 year period. The effect of GFD on diabetic control and growth is still debatable as studies showed a degree of discrepancy in their data. Some studies have reported no change after GFD or no difference from controls in HbA1c[2-4,14,18-27], and this is in agreement with our results. One study reported an increase in HbA1c[15], and few reported a decrease in HbA1c.[28-30] Regarding insulin requirements, most studies have reported no change after GFD or no difference from controls.[4,18-20,28,29] While a few have shown that insulin dose increased after GFD or higher than controls[23,26,27], as has been clearly demonstrated in our study. Concerning BMI, some studies have reported no change after GFD or no difference from controls[2-4,15,19,20,26,27], while we and others showed an increased BMI[23,28], however two other studies showed a decrease in BMI.[14,29]

As in most studies, we used HbA1c to assess metabolic control in our patients. However, there is a need for more reliable assessment of GFD impact on diabetic control, like continuous glucose monitoring, measuring the fluctuation in blood glucose, and the frequency of changes in insulin dose.[23] Our assessment was focused on HbA1c only, which is a crude indicator of subtle glycaemic control, and we could not assess prospectively a better indicator namely continuous blood glucose monitoring.

In diabetic patients, the glycaemic index of carbohydrates is inversely related to glycaemic control.[31] GFD pasta and bread contain higher glycaemic index of carbohydrates than gluten containing products.[23] This can lead to the assumption that GFD could worsen metabolic control in diabetic subjects. Additionally, some expect better glycaemic control prior to diagnosis of CD due to decreased nutrient absorption when CD is active and they expect that the metabolic control to deteriorate as the result of small intestine recovery with an increase in its absorptive capacity.[15] The other argument assumes that introduction of GFD would improve or prevent deterioration of metabolic control by increased diabetic education input or GFD may influence and alter insulin resistance.[28] There is a suggestion that GFD may improve HbA1c by its influence on insulin sensitivity.[30] GFD products are more expensive[29] and less palatable, with less available variety on the market, this may lead to decrease caloric intake and reduce weight gain.[2]

Our finding has shown that the diagnosis of CD in children with type 1 diabetes has no measurable negative impact on the course of diabetes during the study period. However, the double burden of GFD and diabetic diet as well as daily insulin injections does put an extra psychological pressure on the family and the child as well as adding pressure on health resources in providing GFD and educational support. Clinicians are not certain if they are inflicting harm or not by screening for asymptomatic disease with delayed and relatively rare complications in children; delaying the screening for CD until adulthood could be a reasonable solution to minimise deterioration of glycaemic control and quality of life. However, in the current knowledge there is no evidence to support this point of view. Moreover, little is known about the natural history of undiagnosed CD in type 1 diabetes, so the outcomes of GFD on bone mineralization, diabetes control, and quality of life need to be investigated in more details to justify the current screening recommendations.[13]

At present there is insufficient data to support continuing screening asymptomatic patients but long-term collaborative work involving several large-scale national trials are needed to further explore potential benefits and drawbacks of CD screening in diabetic children. However, we believe that reviewing the international guidelines and cancelling CD screening for diabetic children is currently the best option. We also recommend restricting screening only for investigating unexplained symptoms and/or signs related to CD, and screening can be offered later when the child becomes an adult.

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