Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 378–383

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Potential coeliac disease in Type 1 diabetes mellitus: Does a positive antibody lead to increased complications?

J.S. Leeds [a,*], A.D. Hopper [a], M. Hadjivassiliou [b], S. Tesfaye [c], D.S. Sanders [a]

[a] Gastroenterology & Liver Unit, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK
[b] Department of Neurology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK
[c] Department of Diabetes, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

Received 17 November 2012; received in revised form 12 August 2013; accepted 3 September 2013
Available online 23 October 2013

KEYWORDS
Type 1 diabetes;
Glycaemic control;
Coeliac disease;
Complications

Abstract *Background and aims:* Coeliac disease (CD) is more common in people with Type 1 diabetes and is associated with poorer glycaemic control, lipid profiles, nephropathy and retinopathy. Potential CD (positive serology but normal duodenal biopsy) is associated with neuropathy but patients with coexisting Type 1 diabetes were excluded. The aim was to determine whether potential CD is associated with increased microvascular complications in patients with Type 1 diabetes.

Methods and results: Four groups were recruited; 1) patients with Type 1 diabetes and potential CD, 2) patients with Type 1 diabetes and newly identified CD, 3) patients with Type 1 diabetes alone and 4) patients with CD alone. Glycaemic control, quality of life, lipid profile and microvascular complication rates were examined.

As many as 76 individuals were included in the study: 22 in group 1, 14 in group 2, 24 in group 3 and 16 in group 4. There were no differences in age, gender, BMI and diabetes duration between the groups. Patients in group 1 had significantly lower total cholesterol compared to group 3 ($p = 0.003$) but higher than group 2 ($p = 0.027$). There were no significant differences in HbA1c, HDL cholesterol, cholesterol:HDL ratio, creatinine, quality of life scores or prevalence of neuropathy between individuals in group 1 and the other groups.

Conclusions: This is the first study to assess the effects of potential CD in patients with Type 1 diabetes. It appears that an enteropathy is required as well as antibody positivity in order to increase the risk of diabetes related complications. This pilot data requires further longitudinal validation.

Introduction

The association between coeliac disease (CD) and Type 1 diabetes mellitus has been well described with the prevalence of CD ranging between 3 and 5% in the largest studies [1–3]. Recently our group has shown that patients with Type 1 diabetes mellitus and newly identified CD have worse glycaemic control and lipid profiles as well as higher prevalence of microvascular complications. The underlying mechanism was not investigated by this study but the effect upon glycaemic control is likely to be responsible [4].

CD, in the absence of diabetes, is also associated with neurological manifestations with one study showing changes in electroneuromyography even in well controlled CD [5]. These neurological complications can also occur in patients with positive coeliac serology in the absence of enteropathy. Hadjivassiliou et al. looked at gluten ataxia

Abbreviations: CD, coeliac disease; GFD, gluten free diet; DAFNE, Dose Adjustment for Normal Eating; HbA1c, glycated haemoglobin; IgA, immunoglobulin A; HDL, high density lipoprotein; CASE, computed aided sensory evaluator; BMI, body mass index.

* Corresponding author. Room 2.39, Ashgrove House, Department of Gastroenterology, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK. Tel.: +44 114 2261179; fax: +44 114 2712692.
E-mail addresses: j.leeds@nhs.net, jsleeds@hotmail.com (J.S. Leeds).

0939-4753/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2013.09.005

patients and showed that only 13/28 patients had gross histological changes in the duodenum [6]. This offers insight into the role of auto-antibodies as being part of the pathophysiological mechanism. This is separate from gluten sensitivity which is a gluten-mediated immune reaction and gluten allergic reactions which are IgE mediated. Individuals with gluten sensitivity are believed to have a different type of immune mediated reaction and do not have enteropathy but can test positive to antibodies to gliadin [7]. The implications of potential CD to the individual are still unknown as it may be that in time they will develop the histological changes of CD [8,9]. Support for this hypothesis comes from an Italian study of children with Type 1 diabetes, where histological progression was demonstrable following the rectal instillation of gliadin [10]. In gluten ataxia it has been demonstrated that these neurological complications can be arrested or reversed by the institution of a gluten free diet (GFD) [11]. The pathophysiological changes appear to lie in the humoural immune response and a GFD appears to be beneficial [11,12].

Finally recent Swedish work has suggested that individuals with a positive antibody and no enteropathy have an increased mortality when compared to controls [13].

Theoretically there may be benefits to having CD with studies in non-diabetic CD cohorts showing a reduced risk of ischaemic heart disease and hypertension as well as lower cholesterol levels [14,15]. Our previous study showed that patients with Type 1 diabetes and CD had significantly lower cholesterol levels prior to commencement of a GFD [4]. A recent study showed that following a GFD, there was no change in total cholesterol but HDL cholesterol increased by an average of 12% [16]. However, this issue is of more importance to those patients who are already at increased cardiac risk such as those with pre-existing diabetes. In support of this, one study has shown that patients with CD and Type 1 diabetes have a higher rate of subclinical atherosclerosis compared to either condition alone [17].

There is no data in patients with Type 1 diabetes and potential CD particularly with respect to glycaemic control, lipid profiles and microvascular complications. The aim of this study was to examine the effect of potential CD on important outcomes in patients with Type 1 diabetes.

Methods

Study groups

4 specific groups were identified and studied. Group 1: patients with Type 1 diabetes and potential CD (positive antibodies but normal duodenal biopsy), group 2: patients with Type 1 diabetes and newly identified CD, group 3: patients with Type 1 diabetes alone and group 4: patients with newly diagnosed CD but without diabetes.

Participants with type 1 diabetes

The Sheffield Diabetes Centre operates at both the Royal Hallamshire Hospital and the Northern General Hospital. This covers a population of approximately 500 000 and provides tertiary referral services for the South Yorkshire region. There are approximately 2000 patients with Type 1 diabetes defined using the American Diabetes Association position statement [18]. Around 95% of patients with Type 1 diabetes are managed by the diabetes centre in secondary care.

Inclusion criteria were patients with Type 1 diabetes >16 years. Exclusion criteria were age <16 years, inability to consent or diabetes other than Type 1. Where diabetes type was uncertain, the notes were reviewed with the treating consultant and a decision made concerning diabetes type. If diabetes type was still uncertain then the individual was excluded. Patients were prospectively recruited when attending for annual review, foot clinic or Dose Adjustment for Normal Eating (DAFNE) clinic. 1000 individuals with Type 1 diabetes were previously recruited [4] and from this cohort the study groups were identified.

Participants with CD

Patients with newly identified CD were recruited consecutively from the gastrointestinal outpatient's clinic. All patients had biopsy confirmed CD with at least partial villous atrophy (using the modified Marsh criteria) [19] and underwent the neurological investigations prior to commencement on a GFD.

Study group investigations

Study participants completed a health questionnaire and the Short Form 36 (version 2) quality of life assessment questionnaire (QualityMetric Incorporated TM). Data were prospectively collected including age, gender, ethnicity, drug history and other medical co-morbidities. Blood was taken for HbA1c (in the diabetes cohorts), renal profile, ile (including total and HDL cholesterol), full blood count, IgA endomysial antibody, IgA anti-tissue transglutaminase antibody and total IgA level. All participants with either a positive antibody or IgA deficiency underwent duodenal biopsy to confirm the presence or absence of enteropathy.

Retinopathy assessed by notes review and graded as no retinopathy, background changes, pre-proliferative changes or proliferative changes as described by the National Screening Committee for Diabetic Retinopathy [20]. Patients undergo annual retinal photography and were reviewed within 3 months of diagnosis.

All groups were assessed for peripheral neuropathy by a combination of quantitative sensory threshold testing, cardiac autonomic function tests and electrophysiological testing of four nerves. Quantitative sensory threshold testing was performed using the Computer Aided Sensory Evaluator (CASE IV version 4.27) which provides cold, vibration and heat pain detection thresholds on the dorsum of the right foot.

Cardiovascular autonomic function tests are measured using the O'Brien protocol. A 3-lead ECG is attached whilst