Potential reno-protective effects of a gluten-free diet in type 1 diabetes

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Abstract

Aims/hypothesis Coeliac disease is common in type 1 diabetes. It is managed with a gluten-free diet, characterised by foods low in AGEs. We hypothesised that this diet would lead to lower plasma AGEs and be associated with reduced albuminuria.

Methods From a single paediatric clinic, we recruited 21 children with type 1 diabetes and biopsy-proven coeliac disease, and 38 individuals with diabetes alone. The groups were matched for age, sex, duration of disease and metabolic control. Participants completed a detailed clinical and dietary history. Blood samples were taken for HbA_{1c}, coeliac serology, thyroid function, serum IgA levels and plasma AGEs, and urine samples were obtained for estimation of the albumin/creatinine ratio (ACR).

Results All the individuals with coeliac disease were asymptomatic, with negative transglutaminase antibodies. There were no significant differences between the groups in terms of age (14 years), sex (29% male), duration of diabetes (7 years), mean HbA_{1c} (8.3%), lipid levels or treatment regimens. However, children with diabetes and coeliac disease had twofold lower levels of urinary ACR than with those diabetes alone ($p=0.04$). This was associated with lower levels of circulating AGEs ($p=0.03$). These associations were independent of metabolic control, diabetes management and other potentially con-

founding variables, such as household exposure to cigarette smoke.

Conclusions/interpretation Adherence to a gluten-free diet may provide additional benefits for individuals with coeliac disease, and potentially those with type 1 diabetes.

Keywords Advanced glycation end-products · AGEs · Albuminuria · Coeliac disease · Diabetic kidney disease · Diabetic nephropathy · Gluten-free diet · Type 1 diabetes

Abbreviation

ACR Albumin/creatinine ratio

Introduction

Coeliac disease is observed in 4–8% of children with type 1 diabetes [1]. Modern management practices include repeated screening of children with type 1 diabetes, followed by elimination of gluten from the diet in positive individuals. While this is effective in reducing the long-term complications of coeliac disease, its potential impact on diabetic complications had not been previously considered.

AGEs play a significant role in the development of diabetic kidney disease [2]. Recent data suggest that AGEs can be acquired from the diet [3]. The gluten-free diet recommended for individuals with coeliac disease is low in high-temperature processed foods and in flour-based items, which are generally high in AGEs. We hypothesised that a gluten-free diet would lead to lower plasma AGEs in children with coeliac disease and reduced kidney damage compared with matched diabetic patients without coeliac disease.

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Methods

Twenty-one patients with type 1 diabetes and biopsy-proven coeliac disease, on a gluten-free diet for at least 1 year and aged 5 to 18 years were recruited from a single paediatric diabetes clinic at the Royal Children's Hospital (Melbourne, VIC, Australia). Diabetic individuals without coeliac disease were recruited from the same clinic, matched for age, sex, duration of diabetes and glycaemic control ($n=38$). The study was approved by the Royal Children's Hospital Human Research and Ethics Committee. The parents of all participants provided written informed consent.

Clinical details of diabetes and coeliac disease were obtained from clinic notes, including age of onset, duration, family history, hospitalisations, insulin dose and exposure to tobacco smoke (another potential source of exogenous AGEs). All study participants completed a dietary history. Blood samples were taken for HbA_{1c}, total cholesterol, triacylglycerol, serum IgA levels and coeliac serology (anti-gliadin and anti-transglutaminase antibodies). Dietary adherence was determined by negative serum IgA transglutaminase levels. In addition, the fluorescence of albumin, a known marker of AGE modification, was estimated in EDTA-treated blood samples [4]. Urine samples were collected for urinary albumin/creatinine ratio (ACR), measured by size-exclusion chromatography (albumin) and cation exchange high-pressure liquid chromatography (creatinine).

Data are shown as their mean $\pm$ standard error, unless otherwise stated. ACR and AGE-fluorescence were analysed as their log₁₀ derivative. Individuals with and without coeliac disease were compared using unpaired *t* tests and Mann–Whitney tests for non-parametric data.

Results

We examined 21 patients with type 1 diabetes and coeliac disease who had been on a gluten-free diet for at least 1 year (median 4 years, range 1.4–8.4 years). Ten had been

diagnosed on the basis of symptoms and the other 11 detected on the basis of positive anti-gliadin antibodies on screening. At the time of the study, none had persisting anti-transglutaminase antibodies or symptoms, implying nutritional compliance and 'normal' mucosal absorption. Thirty-eight diabetic individuals without coeliac disease, recruited from the same clinic, were matched for age (diabetes alone 14.4 ± 0.4 years; diabetes + coeliac disease 13.8 ± 0.7 years), sex (% male) (diabetes alone, 29%; diabetes+coeliac disease, 29%), duration of diabetes (diabetes alone, 7.0 ± 0.6 years; diabetes + coeliac disease, 7.1 ± 0.2 years) and glycaemic control (HbA_{1c}) (diabetes alone, $8.5 \pm 0.2\%$; diabetes + coeliac disease, $8.2 \pm 0.8\%$). In addition, there were no significant differences in age of onset of diabetes (median 7 years), family history of diabetes (positive in approximately 30–35%), insulin dosing (both 1.0 ± 0.1 IU/kg), body mass index, BMI *z* scores, triacylglycerol levels or total cholesterol levels. However, individuals with coeliac disease were significantly shorter and lighter (diabetes + coeliac disease 53 ± 3 kg) than those with diabetes alone (62 ± 3 kg, $p=0.02$).

Because of their short duration of diabetes, all study participants were normoalbuminuric. However, even within this 'normal range', diabetic individuals with coeliac disease had twofold lower urinary ACR levels than those without coeliac disease (Fig. 1a). Plasma albumin fluorescence was also significantly lower in diabetic patients with coeliac disease than in those without coeliac disease (Fig. 1b). This association was independent of glycaemic and lipid control, the type and intensity of diabetes management, exposure to household tobacco smoke and other potentially confounding variables. However, there was no correlation between albuminuria and albumin fluorescence after adjusting for coeliac disease.

Discussion

Coeliac disease is a common finding in children with type 1 diabetes [1]. Its early identification and management has

Fig. 1 Urinary ACR (**a**) and plasma AGEs (**b**) in individuals with type 1 diabetes with and without coeliac disease. Data show geometric means $\pm$ SEM. **a** DM+CD 0.7 (range 0.5–0.8) mg/mmol; DM alone 1.3 (range 1.0–1.5) mg/mmol. **b** DM+CD 49 (range 45–54) LU/mg albumin; DM alone 85 (range 74–96) LU/mg albumin. DM, diabetes mellitus; CD, coeliac disease. $p<0.05$ for DM alone vs DM + CD. LU, arbitrary fluorescence unit

the primary aim of preventing malnutrition, gastrointestinal symptoms and long-term consequences, which include short stature, osteoporosis and malignancy. We show for the first time that children with type 1 diabetes and coeliac disease have lower levels of urinary albumin excretion compared with matched individuals with type 1 diabetes alone. As urinary albumin excretion is frequently associated with the risk of kidney disease and other long-term complications of diabetes [5], it is possible that coeliac disease or its management confers a degree of reno-protection. However, our results are still preliminary and of low statistical power. Further long-term studies are required to confirm this hypothesis.

The mechanisms by which coeliac disease might reduce urinary albumin excretion remain to be established. None of our patients had reduced serum albumin levels, malnutrition, persisting antibodies or symptoms suggestive of non-compliance or malabsorption. Previous studies have shown there to be no significant changes in HbA_{1c} levels with a gluten-free diet [6], but to cover this possibility we deliberately matched the groups for indices of glycaemia. Similarly, lipid levels, and insulin frequency and dose, were similar in those with and without coeliac disease. It is also possible that the different genetic background between the groups may contribute not only to the development of coeliac disease, but also of kidney disease. Certainly, HLA loci have been associated with diabetic kidney disease [7], which may be under-represented in generally *HLA-DR3*-positive individuals with diabetes and coeliac disease.

A number of studies have demonstrated that AGEs are associated with the presence and severity of diabetic kidney disease, as well as its subsequent progression [2]. Circulating AGEs are also correlated with the dietary intake of modified protein [3]. Greater dietary vigilance in diabetic individuals with coeliac disease probably leads to healthier choices in eating. In addition, a gluten-free diet is low in high-temperature processed foods and flour-based items (such as bread and pasta), making it intrinsically low in AGEs. Consistent with this hypothesis, the circulating level of AGE fluorescence was significantly lower in individuals with coeliac disease (Fig. 1a). Although it did not account for variability in albuminuria in our small study after adjusting for this effect, fluorescence is only a crude marker

for the accumulation of AGEs, most of which are not fluorescent [4].

While a gluten-free diet is the treatment of choice for coeliac disease, it can be very demanding on children and their families to adhere to the restrictions. Furthermore, as many do not suffer overt symptoms, they may lack the motivation to comply. The findings of this study provide additional motivation for dietary adherence for patients with diabetes and coeliac disease. If our findings are confirmed by further prospective and mechanistic studies, exogenous AGE restriction achieved via a gluten-free diet may provide additional reno-protective strategy for all patients with type 1 diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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