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Novel treatment (new drug/intervention; established drug/procedure in new situation)

Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus

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Summary

A 5-year and 10-month old boy was diagnosed with classical type 1 diabetes mellitus (T1DM) without celiac disease. He started on a gluten-free diet after 2–3 week without need of insulin treatment. At the initiation of gluten-free diet, HbA1c was 7.8% and was stabilised at 5.8%–6.0% without insulin therapy. Fasting blood glucose was maintained at 4.0–5.0 mmol/l. At 16 months after diagnosis the fasting blood glucose was 4.1 mmol/l and after 20 months he is still without daily insulin therapy. There was no alteration in glutamic acid decarboxylase positivity. The gluten-free diet was safe and without side effects. The authors propose that the gluten-free diet has prolonged remission in this patient with T1DM and that further trials are indicated.

BACKGROUND

We think that this case report is of great importance because it represents the first human trial of efficiently treating a patient with type 1 diabetes mellitus (T1DM) with gluten-free diet. The potential of an efficient treatment to prolong remission and preserve or regenerate β cells is improvement of the quality of life for many patients and lowering the risk of acute and late complications to T1DM.

CASE PRESENTATION

Introduction

Up to 10% of patients with T1DM also have celiac disorder and, interestingly, the two diseases are by far the most common observed combined, if diabetes is the first to appear, and seldom if celiac disease develops first and gluten-free diet is implemented.[1]

Several attempts have been aimed to delay the loss of β cells, but most studies have shown none[2] or only temporary effects or have serious side-effects. Gluten-free diet may be a promising alternative. In gluten-free-diet-treated non-obese diabetic (NOD) mice never exposed to gliadin, the decline in incidence of T1DM was decreased from 61% to only 6%.[3] The result has been confirmed by several groups and by corresponding studies in BB rats.[4]

Patient

A lean 5-year and 10-month old boy was admitted to hospital after 3 weeks of polydipsia and polyuria, with blood glucose of 14.2 mmol/l, ketonuria, glycated haemoglobin (HbA1c) of 10.4% without diabetic ketoacidosis. Glutamic acid decarboxylase (GAD) antibody was positive, islet cell antibody (ICA) and insulinoma associated antigen-2A (IA-2) were negative. Gliadin, human transglutaminase and endomysium antibodies were also negative. There has been no human leucocyte antigen-typing. He was diagnosed with classical T1DM without celiac disease.

The parents requested a β-preserving treatment and were offered gluten-free diet, because our clinic was preparing a study with such an intervention. The parents were offered guidance and advice on gluten-free diet and wished to start the therapy on their own, but with the control visits and meal stimulated tests as planned for the coming project on gluten-free diet for newly diagnosed patients with T1DM.

Our patient was treated with insulin for a total of 5 weeks with the mean insulin requirement of 0.69 IE/kg/24 h. At the end of the 5 weeks the insulin requirement declined, and the patient entered the remission phase without any insulin requirement for the following 3 weeks, with blood glucose values in the range 4–6 mmol/l. Gluten-free diet was initiated 8 weeks postdiagnosis. HbA1c was at this time 7.8% and 12 weeks postdiagnosis 6.7% (ref. range 4.3%–5.8%). His diet before the gluten-free diet was normal with preference for pasta, burger and pizza like most children at his age.

Following nutritional advice, the patient was started on a gluten-free diet with a low glycemic index. The average calorie intake was 7085 KJ/day split into six to seven courses, with 24% energy from carbohydrates, 26% from protein and 49% from fat. HbA1c levels were stabilised at 5.8%–6.0% without insulin therapy. Fasting blood glucose was maintained at 4.0–5.0 mmol/l. The patient gained 1.1 kg and 6 cm in height over 1 year.

Stimulated C-peptide and proinsulin were tested after an individualised mixed meal (including 35–39 g carbohydrates, 5–7 g protein and 3–3.5 g fat) 8 and 12 months after diagnosis. At 8 months postdiagnosis, stimulated C-peptide was 580 pmol/l, stimulated proinsulin was 26 pmol/l. At 12 months postdiagnosis, fasting and stimulated C-peptide levels were 2 and 147 pmol/l (figure 1A, patient highlighted in red) respectively, and proinsulin 15 pmol/l. C-peptide test was preformed with Immulite2500 C-peptide. Auto-antibody titres (GAD, ICA and IA-2) were unaltered. At 16 months postdiagnosis, the fasting serum

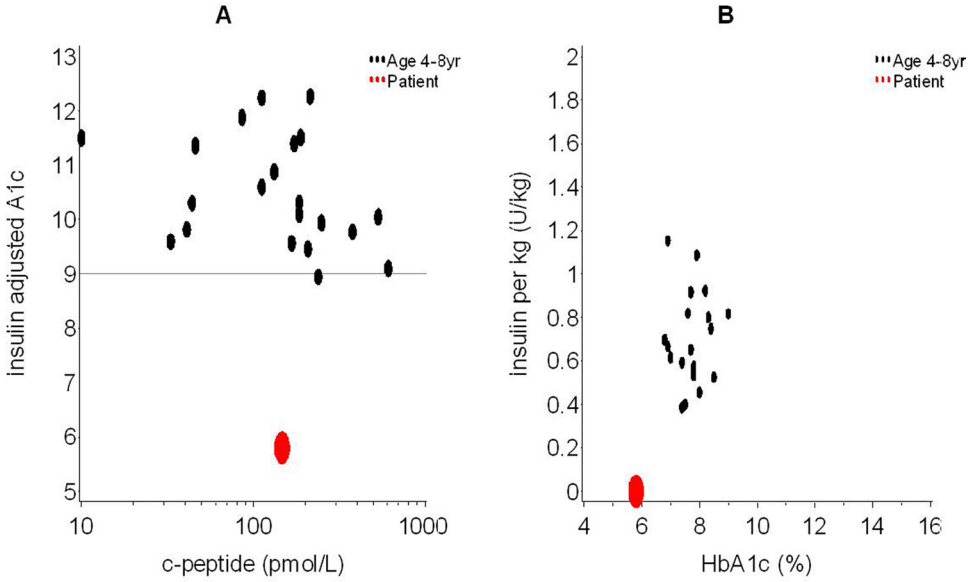

Figure 1 (A) Insulin adjusted A1c% in the index patient (in red) and in 21 other diabetic children (matched by age and diabetes duration) aged 4–8 years (in black) against stimulated C-peptide pmol/l. Insulin adjusted A1c ≤9% indicates remission. (B) Insulin requirement mmol/l for the corresponding HbA1c% after 12 months.

insulin was 4.6 pmol/l with blood glucose of 4.1 mmol/l and lipids were all normal. At 20 months postdiagnosis, the patient is still in no need of daily insulin therapy.

DISCUSSION

The patient was diagnosed with T1DM based on the high HbA1c at onset and autoantibody positivity, without clinical or paraclinical indicators of celiac disease. At present time, the patient has been without daily insulin therapy for 20 months, a feature rarely seen in children of this age. None of the children aged 4–8 years from the Danish cohort (a total of 21 patients diagnosed in 2004/2005, matched by age and diabetes duration), represented in figure 1A, B have a none-insulin recorded at visit 3, 6 or 12 months after onset. Despite the long remission period on a gluten-free diet, there has been no alteration in GAD positivity, in agreement with previous studies.

By personal communication with the scientist (Andersen MLM, 2012) studying a historic cohort (524 children from 12 European countries and the USA), we know that children with T1DM at the age 6–7 years old show a decline in stimulated C-peptide of 10% per month. The patient described in this case report shows a decline in stimulated C-peptide over time from 580 to 147 pmol/l in 4 months, which is an average decline of more than 10% per month.

Even though the patient has a low stimulated C-peptide after 12 months, he still displays a low insulin adjusted A1c, a surrogate marker for residual β-cell function,[5] compared with the Danish cohort shown in figure 1A. Remission has been defined dependent on either HbA1c ≤7.5%, a daily insulin requirement of ≤0.5 units/kg/24 h or C-peptide above 300 pmol/l. The alternative definition of insulin adjusted A1c≤9 is suggested by Mortensen *et al*[5] including both HbA1c and insulin dose. By this definition the patient is still in remission with insulin adjusted A1c of 5.8, despite the low stimulated C-peptide. Using the insulin adjusted A1c as in figure 1A, gives a more accurate base for comparing our patient with the cohort, as he is in no need of exogenous insulin and the cohort has a deviating insulin requirement from prox. 0.4–1.2 units/kg/24 h (figure 1B).

The reason for the significant decline in stimulated C-peptide seen in our patient might be due to a lower glycaemic index in the individualised meal compared with the standard mixed meal used in the Danish cohort ingested before blood sampling. The blood glucose of the patient after stimulation was within normal range: 7.1 and 8.1 mmol/l at first and second testing, respectively, which is not seen in patients with T1DM after stimulation. As C-peptide and stimulated blood glucose are both low, his need of insulin might be lower than age-matched children observed in the Danish cohort, which indicate a high insulin sensitivity in our patient. The reason why the patient was not exposed to a standard mixed meal with high glycaemic index, was the parents' fear of additional β-cell stress and consequently provoking a premature end of the remission period.

The patient has a low calorie intake 7085 KJ/day which is below the mean recommended 8400 KJ/day for a boy of this age and height, though within the normal range and he continues to follow his growth trajectory.

The prolonged remission may be due to the gluten-free diet, the low dietary glycaemic index, the distribution of small meals throughout the day, or a combination thereof. Results from animal models suggest that gluten-free diet is a likely cause.[3 6]

CONCLUSION

A child with classical newly diagnosed T1DM started on a gluten-free diet, remains without the need for exogenous insulin after 20 months. The gluten-free diet is safe and without side effects. We propose that the gluten-free diet prolonged remission in this patient with T1DM and that further trials are indicated.

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Learning points

- Gluten-free diet prolongs remission.
- Gluten-free diet increases insulin sensitivity.
- Gluten-free diet is safe and acceptable.

Competing interests Stine Møller Sildorf: stock ownership at NovoNordisk. Jannet Svensson: stock ownership af NovoNordisk

Patient consent Obtained.

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