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Does a gluten-free diet lead to better glycemic control in children with type 1 diabetes? Results from a feasibility study and recommendations for future trials

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ABSTRACT

Background: Increasing evidence suggests a link between type 1 diabetes (T1D) and intake of gluten, but no controlled trials have examined whether a gluten-free diet (GFD) has positive effects on glycemic control in children with T1D.

Methods: We conducted a non-randomized feasibility study. Twenty-three children with newly diagnosed T1D were included and either followed a GFD (n = 14) or a normal diet (n = 9) for 12 months. Effects of diet on glycemic control were examined by measuring insulin production (c-peptide), hemoglobine A1c (HbA1c) and insulin dose adjusted A1c (IDAA1c). Degree of adherence to the GFD and effects on quality of life were also examined.

Results: Children on a GFD showed a statistically significantly lower HbA1c at six months (P = 0.042) compared with children on a normal diet and point estimate differences indicated better glycemic control in the GFD group at 6 and 12 months. Adherence to a GFD varied but was satisfactory for a majority of children. The GFD group reported poorer quality of life at inclusion and there was a non-significant difference for quality of life between groups throughout the study.

Conclusions: A strict GFD can be maintained by children with newly diagnosed T1D and may have positive effects on glycemic control. Our findings should be interpreted carefully because of small samples and possible confounding. We provide recommendations for future trials and suggest using a randomized-controlled design with 30–40 participants in each arm.

1. Background

Type 1 diabetes (T1D) is an autoimmune disease in which the immune system breaks down β-cells and thus the body's ability to produce insulin. Despite extensive research, the etiology of T1D is largely unknown. Exogenous insulin is an effective treatment but demanding and not without complications [1]. Several studies have shown the importance of good glycemic control to avoid long-term diabetic complications and that a partial endogenous insulin production facilitates a good glycemic control [2]. In the Diabetes Control and Complications Trial, even quite modest residual insulin secretion (i.e., a β-cell stimulation with serum C-peptide > 0.20 pmol/ml) played an important role in preventing complications [3]. Thus, a major interest in trials of T1D is the preservation of β-cell function. Numerous studies have been designed to slow down the destruction of the β-cells, most often by altering the immune system, but perhaps with the exception for two promising studies on antithymocyte globulin [4], no safe, long-term results have emerged [5].

Genetic factors have been estimated to contribute to around 50% of the risk of T1D [6] The genes most strongly associated with the risk to

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develop T1D are HLA DQA1*05-DQB1*02 (DQ2) and DQB1*0302 (DQ8). These HLA-alleles also confer risk for celiac disease (CD). Accordingly, patients with T1D are at increased risk to develop CD [7]. The treatment for CD is lifelong avoidance of any products containing gluten.

Growing evidence suggests, not only a genetic connection between T1D and CD, but also between a higher gluten consumption and increasing T1D incidence. For example, a recent study on gluten intake in pregnant women showed the risk of T1D in offspring increased proportionally with higher gluten intake [8]. In another study, a six month GFD improved insulin secretion in subjects at high risk for T1D [9]. Moreover, a small Danish pilot study, that included 15 children with newly diagnosed T1D showed significant improvement of glycemic control measured by HbA1c and IDAA1c following a one-year GFD [10].

Animal studies also support a link between gluten and T1D. There is evidence to suggest that gluten influences β-cells and other important components with possible links to the evolvement of T1D. These components include pro-inflammation, the innate and adaptive immune system, gut microbiota and gut permeability [11–16]. Besides potentially activating an autoimmune response that can cause destruction of β-cell islets, and thereby the production of insulin, gliadin itself is now known to reach pancreas [17], which may induce inflammation [13] and β-cell stress [14]. A study on mice showed that the incidence of T1D was reduced from 64% to 15% following a lifelong GFD [18]. Several other studies on non-obese diabetic mice have also shown a reduced risk of autoimmune diabetes as an effect of a GFD [15,18,19] [20].

In sum, increasing evidence suggests that a GFD may have positive effects on T1D pathology, onset and clinical course. However, studies on humans are rare. The primary aim of the present study was therefore to investigate effects of a GFD on glycemic control by measuring insulin production (c-peptide), hemoglobine A1c (HbA1c) and insulin dose adjusted A1c (IDAA1c) in children with newly diagnosed TID. In line with previous research, our hypothesis was that a GFD would have positive effects on glycemic control and c-peptide. Secondary aims were to examine adherence to a GFD and effects on diabetes-related quality of life. Since inclusion proved to be harder than expected, the current study data are reported here in the form of a feasibility study.

2. Methods

2.1. Design and ethics

The study was designed as a clinical 2-arm (GFD versus normal diet (ND)) feasibility study of children (3–61 years) with newly diagnosed T1D. Group allocation was based on family choice. Randomization was not employed because it was assumed to influence compliance. Inclusion criteria was newly diagnosed T1D (<2 months) according to the diabetes classification of the American Diabetes Association [21]. Patients with diagnosed CD and children lacking the HLA alleles DQA1*05-DQB1*02 [DQ2] or DQB1*0302 [DQ8] were not included.

The study protocol was reviewed and approved by the Regional Ethical Board at Lund University (Registration number: 2014/349, 20140808) and registered at Clinical Trials (03037190; https://clinicaltrials.gov/ct2/show/NCT03037190). Consent forms were signed by all caregivers and/or patients in accordance with the Declaration of Helsinki.

2.2. Procedure

Inclusion for the overall study started in October 2015. Patients are recruited from the pediatric clinics in Lund and Malmö at Skåne University Hospital and information about the study is given orally and in writing to eligible patients and their caregivers. These clinics see around 50 children with newly diagnosed T1D (3–16 years of age) annually. As a clinical routine, we analyze tTG-ab and perform HLA typing for DQ2 and DQ8 in all children and adolescents at diabetes diagnosis. Among children with newly diagnosed T1D in Sweden, around 3% have known CD and around 10% lack DQ2 and DQ8.

Patients included in the study are followed for 24 months and are assessed at six clinical visits: inclusion (visit 1); 3 months (visit 2); 6 months (visit 3); 12 months (visit 4); 18 months (visit 5); and 24 months (visit 6). Patients in both the GFD and the ND groups have appointments with a dietician as a clinical routine at 3, 6, 12, 18 and 24 months. Patients in the GFD group have one extra appointment for advice and information concerning a GFD at inclusion in the study. The GFD groups appointments are longer at 3, 6 and 12 months since adherence to a GFD is assessed.

The study aimed to include 80 patients in each group. However, inclusion of patients has been very difficult (which is considered further in the Discussion section). Therefore, the present report takes advantage of existing data in the form of a feasibility study. Data for all participants that had undergone the 12-month assessment as of June 2020 are reported.

2.3. Measures

2.3.1. Primary outcomes

The primary outcome measures were glycated hemoglobin A1c (HbA1c), insulin dose adjusted A1c (IDAA1c), and C-peptide levels. HbA1c was analyzed using CAPILLARYS 3 TERA Hemoglobin A1c Kit-program where separation is on capillaries. Separation is optimized to eliminate interferences from variants of hemoglobin, pre- HbA1c and carbamylated hemoglobin. The instrument analyzes 68 samples per hour. Detection is at 415 nm [9,10]. HbA1c and IDAA1c were used to evaluate glycemic control. IDAA1c was calculated from insulin use and HbA1c (4 x insulin dose/kg/24 h + HbA1c in %). C-peptide levels were measured in duplicates using commercial ELISA (Mercodia, Uppsala, Sweden) according to the manufacturer's instructions. Optical density was measured at 450 nm in a FLOUstar Optima 96-well plate reader (BMG Labtech Gmbh, Ortenberg, Germany). Inter- and intra-variation ranged between 0.6-4.8% and 2.9–4.8%, respectively. The detection limit of the assay was reported to be 25 pmol/L. C-peptide and blood-glucose were assessed using a Mixed Meal Tolerance Test (MMTT) at 0, 30, 60, 90 and 120 min at all visits. For the MMTT, Fresurbin Original Drink of 200 ml (200 Kcal; 7.6 g protein; 6.8 g fat; 27.2 Cho/Kg/g) was used. The patients were classified into three risk groups based on their HLA-DQB1 genotype: high risk = DQ2/DQ8, DQ8/DQ8 and DQ2/DQ2, moderate risk = DQ8/DQX; where x indicates all other alleles except DQ2 or DQ8, low risk = DQ2/DQX; where x indicates all other alleles except DQ2 or DQ8.

2.3.2. Adherence in the GFD group

Adherence to a GFD was evaluated at 3, 6 and 12 months using the questionnaire from Green, Expert Dietician Evaluation of Gluten-Free Diet Adherence for Children. According to the Green measures, adherence is scored across five categories: Excellent, Good, Fair, Poor and Not gluten free [22]. Excellent and good are considered indicative of a patient following a GFD.

2.3.3. Quality of life

A validated questionnaire assessing QoL was completed by caregivers and/or patients at all visits (either the DISABKIDS 3–7 years or the DISABKIDS 8–15 years) [23]. The diabetes module of the questionnaire was analyzed. This module includes 10 questions covering how T1D affects QoL. The ten items are summed into a total QoL score. Higher scores indicate more diabetes-related problems with QoL. In our study, the internal consistency of the diabetes module items was adequate at all time points (Cronbach's alpha ranging from 0.73 to 0.84).

2.4. Statistical analysis

Group comparisons (GFD vs ND) for our outcome measures (C-

peptide, HbA1c, IDAA1c and DISABKIDS) were carried out at baseline and at 3, 6 and 12 months. Because of the small groups, data could not be assumed to be normally distributed and non-parametric statistical tests were used (Mann-Whitney U tests). Because of the small groups and low statistical power to detect true group differences (i.e., high risk of Type 2 errors), we estimated between-group effect sizes at each time point in the form of the Rank-Biserial Correlation. This measure can be interpreted as a correlation between group (i.e., GFD vs ND) and the outcome variable (i.e., C-peptide, HbA1c, IDAA1c and DISABKIDS) with higher values indicating that the ND group has higher scores. A correlation above 0.4 is often considered a moderate effect and a correlation above 0.6 a strong effect.

2.5. Missing data

As further described below, five participants withdrew from the study. Thus, missing data were present for these participants after their last visit. Further, three C-peptide values were missing at select time points in the GFD group and at one time point in the ND group. Adherence ratings in the GFD group were missing for one participant at the 3, 6 and 12 month visits. Missing data were excluded when performing all analyses.

3. Results

3.1. Participants

In the present study, data from 23 children included between October 2015 and April 2019 were analyzed. Fourteen children were included in the GFD group and 9 in the ND group. In the GFD group, one child dropped out after the baseline visit and two children after the 6 month visit. In the ND group, one child dropped out after the 3 month visit and one child after the 6 month visit. Participant data are presented in Table 1.

3.2. HbA1c

At 6 months, there was a statistically significant group difference for HbA1c with a lower mean value in the group on gluten free diet (see Table 2). Further, the point estimate differences (and the within-group variation) between the GFD and ND groups at 6 and 12 months indicated a moderate to strong effect of group (Rank Biserial Correlations ~ 0.5), with the GFD group showing lower levels of HbA1c at 6 months (44.2 vs 49.6) and at 12 months (44.6 vs 49.7). In Fig. 1, each individual trajectory of HbA1c levels across the study together with group means are presented. The ND group showed temporally stable levels, while there was a trend for a decrease in the GFD group.

Table 1
Background and baseline data across study groups.

	Gluten-free diet	Normal diet	*p*
	n = 14	n = 9	
Age at inclusion, median (IQR)	9.30 (6.83)	8.72 (7.10)	.926
Age at onset, median (IQR)	9.14 (7.29)	8.48 (7.13)	.896
Gender, females, n (%)	8 (57%)	6 (67%)	.648
Human Leukocyte Antigen*			
High risk, n (%)	8 (62%)	3 (33%)	
Medium risk, n (%)	5 (38%)	4 (44%)	
Low risk, n (%)	0 (0%)	2 (22%)	
Autoantibodies[12]			
GAD, positive, n (%)	6 (46.2%)	3 (33.3%)	
IA2, positive, n (%)	11 (84.6%)	8 (88.9%)	

Note. GAD = Glutamic Acid Decarboxylase. IA2 = Islet Antigen number 2. [1]No statistical comparison was carried out due to the low *n*. [2]One individual may be positive for both antibodies.

Table 2
Results for the gluten-free and the normal diet group for glycated haemoglobin, HbA1c, insulin dose adjusted A1c (IDAA1c), C-peptide and quality of life at inclusion, 3, 6 and 12 months. Negative Rank-Biserial Correlations indicate that the GFD group has lower values.

	Gluten-free diet (GFD)		Normal diet (ND)		*p*	Rank-Biserial Correlation
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
HbA1c						
Inclusion	48.93 (9.19)	47.00 (12.00)	49.78 (7.41)	48.00 (6.00)	.659	−0.119
3 months	45.31 (9.38)	42.00 (12.00)	49.00 (9.17)	48.00 (14.00)	.284	−0.282
6 months	44.18 (6.37)	44.00 (6.00)	49.63 (4.69)	49.50 (9.00)	.042	**−0.568**
12 months	44.55 (5.89)	43.00 (6.00)	49.71 (6.53)	48.00 (15.00)	.091	**−0.494**
IDAA1c						
Inclusion	7.25 (1.47)	7.17 (2.24)	7.70 (1.06)	7.48 (1.48)	.516	−0.175
3 months	7.38 (1.34)	6.99 (2.06)	7.76 (1.19)	8.04 (2.22)	.471	−0.197
6 months	7.17 (0.93)	7.09 (1.72)	8.39 (1.81)	7.76 (2.22)	.177	**−0.386**
12 months	8.08 (0.97)	7.64 (1.74)	8.75 (0.97)	8.75 (1.05)	.104	**−0.481**
C-peptide						
Inclusion	0.46 (0.36)	0.41 (0.49)	0.52 (0.28)	0.47 (0.36)	.571	−0.151
3 months	0.33 (0.22)	0.37 (0.45)	0.45 (0.27)	0.36 (0.54)	.373	−0.241
6 months	0.33 (0.18)	0.33 (0.28)	0.35 (0.22)	0.33 (0.35)	1.000	−0.000
12 months	0.21 (0.12)	0.21 (0.18)	0.26 (0.16)	0.23 (0.23)	.585	−0.183
Quality of life						
Inclusion	15.42 (6.85)	15.00 (10.00)	11.85 (2.48)	12.22 (3.89)	.155	**0.365**
3 months	13.16 (4.79)	15.56 (4.17)	11.81 (2.84)	12.22 (4.17)	.363	0.250
6 months	12.53 (5.71)	12.22 (6.67)	10.14 (2.33)	10.00 (2.78)	.198	**0.364**
12 months	12.63 (4.34)	12.22 (6.67)	9.52 (3.84)	8.89 (6.66)	.188	**0.390**
B-glu at 90 min during MMTT						
Inclusion	13.53 (4.86)	12.50 (5.67)	11.60 (2.79)	11.20 (3.50)	.270	**.286**
3 months	15.18 (2.79)	15.10 (5.20)	14.30 (4.78)	12.70 (7.80)	.526	**.171**
6 months	16.25 (2.60)	16.65 (4.22)	16.71 (2.78)	16.25 (4.70)	.824	**-.075**
12 months	17.07 (4.47)	16.25 (9.13)	18.78 (3.20)	18.85 (3.90)	.368	**-.300**

Note. Mann-Whitney U tests were used to compare groups. Effect sizes are presented in the form of the Rank-Biserial Correlation. Moderate and large effect sizes, i.e., Rank-Biserial Correlation >0 .3, are highlighted in bold. IQL = Interquartile Range. SD = standard deviation.

3.3. IDAA1c

Regarding IDAA1c levels, the GFD and ND groups did not differ statistically significantly at any time point (see Table 2). However, point estimate differences (and the within-group variation) at 6 and 12 months corresponded to medium to large effect sizes (Rank Biserial Correlations ~ 0.4), with the GFD group showing lower levels at both 6 months (7.2 vs 8.4) and 12 months (8.1 vs 8.8). In Fig. 2, each individual trajectory of IDAA1c levels across the study's assessments together with the group means are presented. The ND group showed a trend for increasing levels between 3 and 12 months, while the GFD group showed increasing levels only between 6 and 12 months.

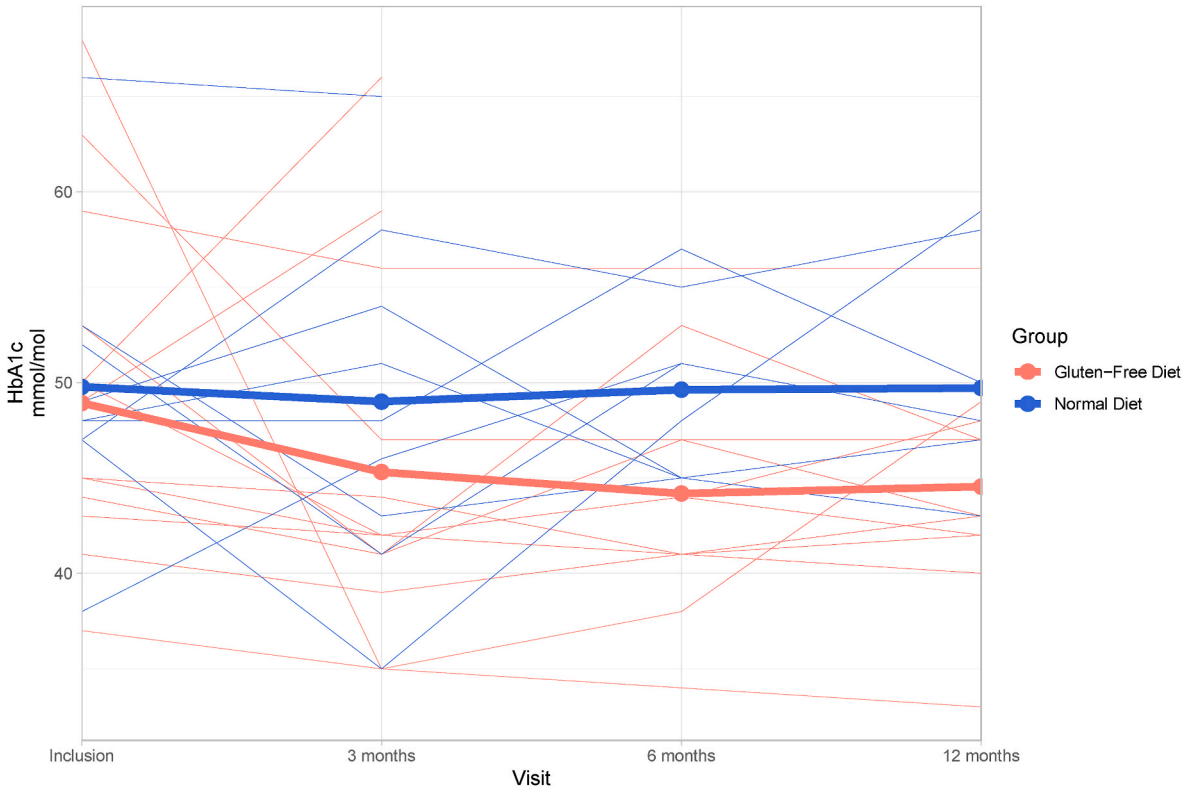

Fig. 1. HbA1c at baseline and follow-ups for study groups.
Please note that the x-axis is truncated between the 6 and the 12 month timepoints.

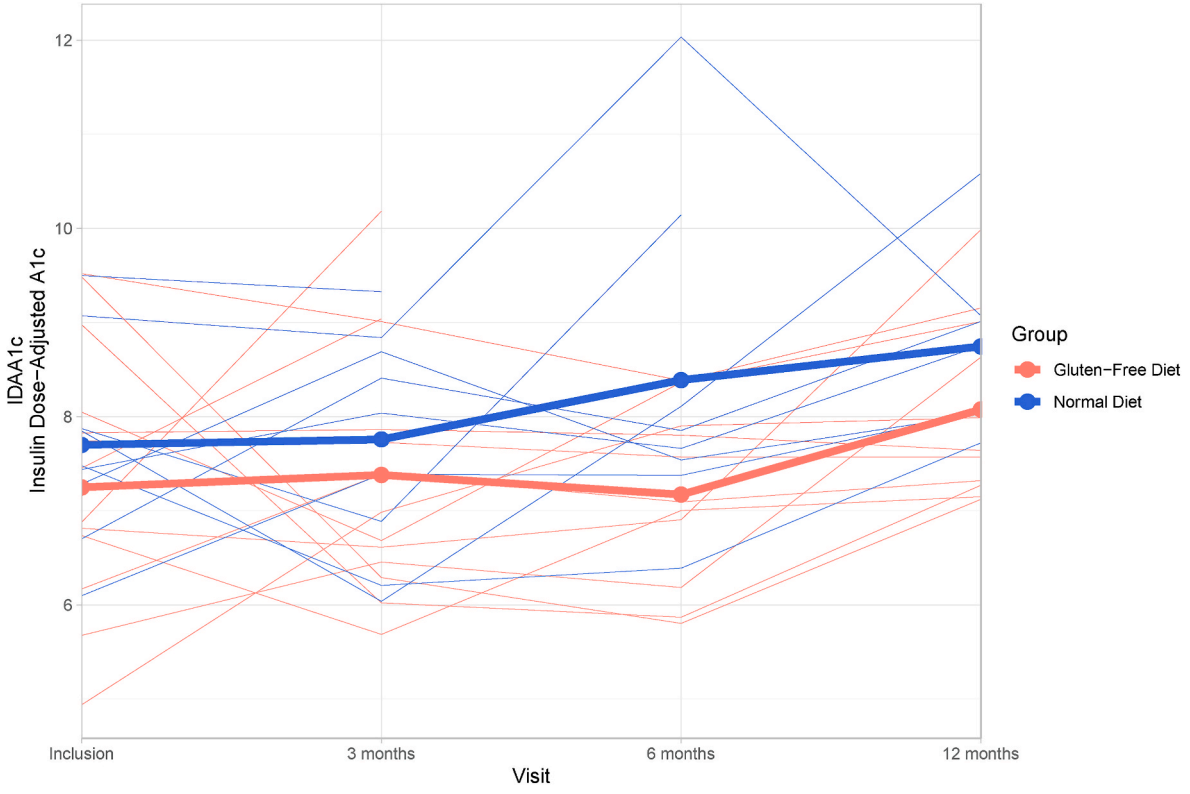

Fig. 2. IDAA1c at baseline and follow-ups for study groups.
Please note that the x-axis is truncated between the 6 and the 12 month timepoints.

3.4. C-peptide

For C-peptide, no statistically significant differences were present between groups at any time point (see Table 2). Further, small point estimate differences were present at all time points. Each individual trajectory together with group means are presented in Fig. 3. Both groups showed a trend of a decrease in C-peptide values over time.

3.5. Adherence

At 3 months, two GFD participants (17%) scored excellent adherence, nine (75%) good adherence and one (8%) fair adherence. At 6 months, two participants (20%) scored excellent adherence, seven (70%) good adherence and one (10%) fair adherence. At 12 months, three participants (30%) scored excellent adherence, six (60%) good adherence and one (10%) fair adherence. These ratings corresponded to satisfactory adherence for 92% of participants at 3 months, 90% at 6 months and 90% at 12 months or 85%, 69% and 69% if participants that withdrew from the study were classified as not following a GFD.

3.6. Quality of life

No statistically significant differences emerged between the groups in relation to diabetes-related QoL (Table 2). However, at all time points, the GFD group showed higher point estimates, indicating more diabetes-related problems with QoL, with moderate to large effects sizes at all time points.

3.7. Post hoc examination of blood glucose levels

Because we found some evidence suggesting potential benefits of a GFD on HbA1c and IDAA1c while no difference was found in relation to C-peptide, we conducted a post hoc examination of 90 min blood glucose (B-glu) levels during MMTT across visits for the two groups. Results are in Table 2 and Fig. 4. The GFD group had numerically higher values at inclusion but lower values at the 12 month visit. These differences were not statistically significant, but the point estimate differences indicated a moderately sized difference between groups.

4. Discussion

The aim of the present study was to examine whether a GFD may have positive effects on glycemic control in children with newly diagnosed T1D. Because of the difficulties to recruit patients, this study was carried out as a feasibility study. Accordingly, important secondary aims were to examine adherence to a GFD and whether a GFD affected diabetes-related QoL. Finally, because the study proved difficult to conduct, we convey our experiences regarding difficulties with including patients, and provide recommendations for how to best conduct future trials.

A statistically significant group difference for HbA1c at 6 months showed better glycemic control in the GFD group. No other statistically significant group differences emerged which was expected because of the small groups and thus an increased risk of Type 2 errors. Because of the low statistical power, we interpreted group differences according to estimated effect sizes for the differences (which are less sensitive to sample size). Inspecting the effect sizes, further support for potential benefits of a GFD emerged. Specifically, possible positive effects were found in relation to HbA1c and IDAA1c levels at the 6 and 12 month visits while no substantial differences were found for decreases in C-peptide.

These findings add to a small body of literature suggesting that the exclusion of gluten for children with T1D may have beneficial clinical effects. However, the expected C-peptide decrease, mirroring a weakening insulin response, was not attenuated in the GFD group. Hence, the effects on glycemic control cannot be explained by a sustained insulin production. Instead, the effects may result from an increased insulin sensitivity, which is in line with results from a study where pre-diabetes

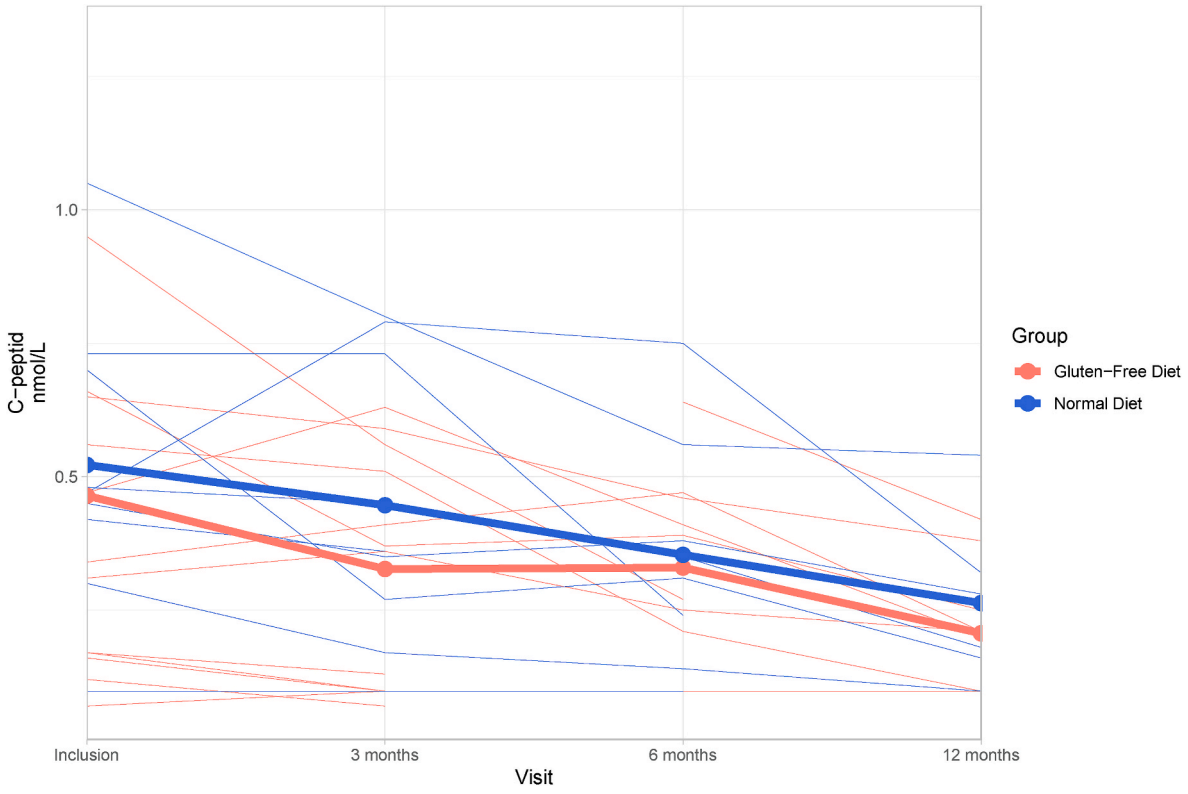

Fig. 3. C-peptide at baseline and follow-ups for study groups.
Please note that the x-axis is truncated between the 6 and the 12 month timepoints.

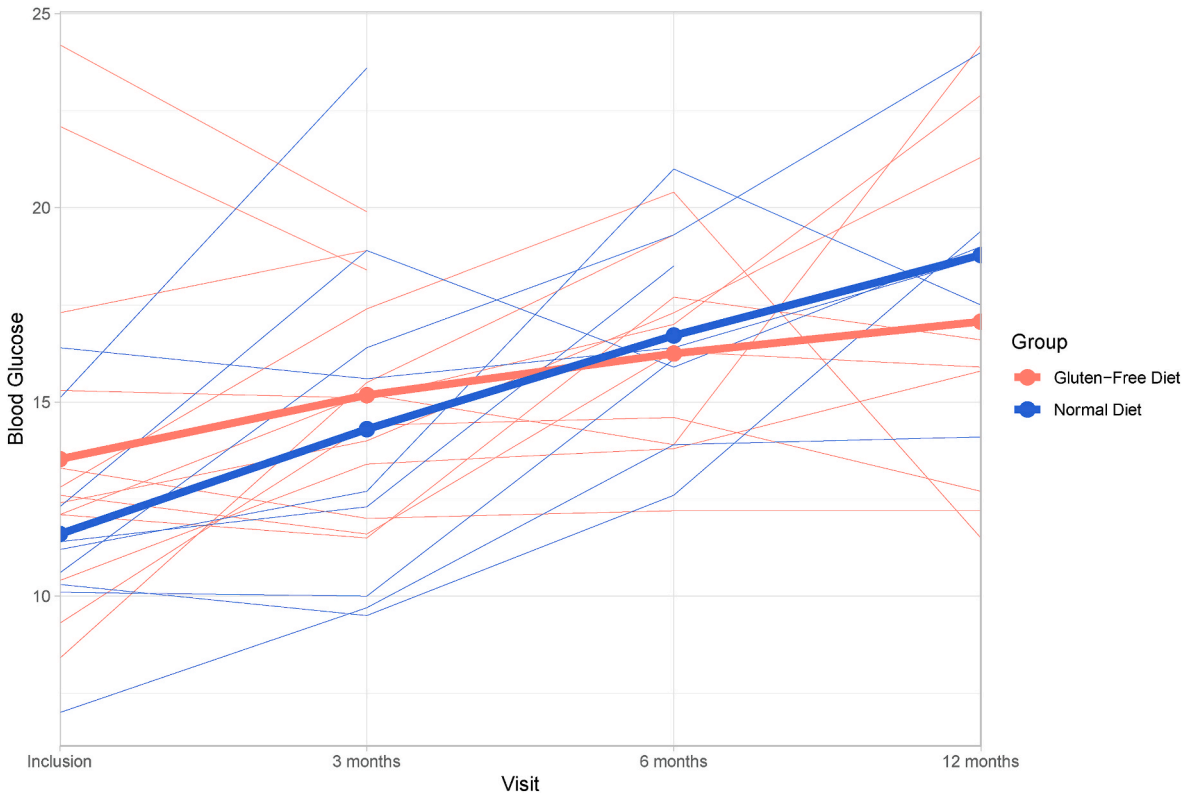

Fig. 4. Blood glucose at baseline and follow-ups for study groups.
Please note that the x-axis is truncated between the 6 and the 12 month timepoints.

individuals on a 6 month GFD showed improved insulin sensitivity [9]. To further examine the effects of a GFD on glycemic control, we conducted post hoc analyses of P-glucose levels during MMTT and found lower P-glucose in the GFD group. Because P-glucose is measured during MMTT, it is not dependent upon a possible confounding of different food sources (and their potentially different effects on blood sugar levels). Therefore, lower P-glucose levels in the GFD group further support a better glycemic control in this group, possibly explained by an enhanced insulin sensitivity.

Adherence to a GFD varied. At 12 months, 69% of patients reported satisfactory adherence to a GFD. However, if the children who withdrew from the study were excluded, satisfactory adherence was high, with 90% adhering to a GFD at 12 months. This suggests that a GFD is feasible for a majority of children with newly diagnosed T1D, at least among those who chose to participate in this study.

Regarding QoL, no firm conclusions can be drawn as the groups had different scores at inclusion and continued to differ throughout the study. Previous studies have found no differences in QoL in T1D children with and without CD [24]. If stronger evidence of effects of a GFD in relation to glycemic control in T1D is established, this is expected to result in beneficial effects also on QoL. However, the introduction of a GFD to children that does not have CD may affect QoL negatively, as adherence to a GFD is demanding. We recommend future trials to examine QoL alongside outcomes of glycemic control.

The present results need to be interpreted in the light of two major limitations. First, small groups gave us weak statistical power to detect (or reject) group differences. This was due to difficulties with recruitment (discussed below). Second, participants were not randomized. This introduces uncertainties about outcomes because factors (e.g., patient characteristics) that affect the choice to participate (and in which group to participate) may have affected outcomes (i.e., confounding). These two limitations are discussed below.

We aimed to include 80 patients in each group, but after three years, only 23 patients had been included, corresponding to around 10% of the potentially eligible patients. The reasons for the difficulties with recruitment are largely unknown but based on our local knowledge of the trial, few eligible patients were invited to participate. One reason for this may be a reluctance among physicians to ask newly diagnosed children with T1D, in itself a burdensome disease with high impact on day-to-day life, to participate in a trial that would introduce a global change in diet as well as repeated blood samples. To promote the study, we sent a letter to each eligible physician. A partly related explanation could be that we did not promote the study enough to physicians working with children with newly diagnosed T1D. Given that a vast majority of children that participated were included by the physician responsible for the study supports this notion. Future trials need to secure that eligible patients are invited and perhaps it is best that a trial coordinator makes contact with all eligible patients and invites them to participate. Finally, it may be important to thoroughly educate and inform both physicians and patients about the rationale behind the study to make them more prone to participate.

We would also like to address the issue of randomization. A non-randomized design was selected because we believed that randomization may result in a low adherence to a GFD. What we did not consider enough was that reasons driving families to accept a burdensome global diet change may act as an important confounder. It is possible that families that were highly motivated to adjust everyday life in accordance with the new demands of having a child with T1D were more prone to enter the GFD group. Thus, other factors that could improve metabolic control, such as overall healthier food and more exercise, may explain the promising results found for a GFD in this study. It would have been interesting to evaluate differences in food choices when on a GFD. It is possible that a GFD reduces the intake of some foods which are difficult for patients with T1D to handle; however, a previous study has shown that a change to a GFD does not necessarily include a change of food groups [25]. Further, GFD foods often have a high glycemic index

[26,27], which is not favorable for patients with T1D, but since the GFD group had longer follow-up visits with a dietician such challenges may have been managed successfully. It is also possible that the extra time spent with a dietiscian may have resulted in healthier foods in general which in that case could be an explanation for the better glycemic control found in the GFD group.

As in most clinical intervention studies, we had dropouts, with a total of five patients not completing the study as intended. After the three-month assessment, three patients with high HbA1c dropped out; two in the GFD group and one in the ND group. This may have affected outcomes. Nevertheless, since several of the participants individual HbA1c levels fluctuated over time, it is hard to speculate about whether, and how, the dropouts affected study results. It is important that studies with more participants carefully examine how dropouts affect results, for example by using last observation carried forward or multiple imputation.

Taken together, we recommend future trials to use a randomized-controlled design. Based on the point estimate group differences in this study, designs with 30 patients in each arm (GFD and ND) would give about 80% power ($a = 0.05$) to detect the smallest clinically significant effect in our study (IDAA1c at 6 months). The largest effect in our study (HbA1c at 6 months) could be detected, using the same power and alpha levels, with as few as 20 participants in each arm.

5. Conclusion

Despite limitations, we consider the present results to be important. To our knowledge, there is only one other intervention study examining effects of a GFD in relation to T1D in children, and that study was carried out without a control group [10]. Using a control group, our results indicate possible benefits of a GFD in relation to glycemic control. Our results also suggest a moderate to good capacity to maintain a strict GFD once this diet has been initiated. We found no evidence that following a GFD had detrimental effects on diabetes—relatedQoL, but these results should be interpreted carefully because of group differences at inclusion. Families that selected to follow a GFD may have been more motivated to adhere to broader treatment regimens and lifestyle changes in accordance with recommendations after the diagnosis of T1D, which may have influenced the differences in HbA1c. A randomized-controlled design would circumvent this possibility and 30–40 participants in each arm in such a trial may be sufficient to detect true effects of a GFD on glycemic control in children with T1D.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Regional Ethical Board at Lund University (Registration number: 2014/349, 20140808). Consent forms were signed by all patients and their caregivers in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

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Strobe

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Authors' contributions

MD HS helped design the study, carried out statistical analyses and drafted and edited the manuscript. Dr. MC carried out statistical analyses and edited the manuscript. Drs. IT, JD, MH and FN edited the manuscript. MD Dr AC designed the study and edited the manuscript. All authors have read and approved the manuscript.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Abbreviations

T1D	Type 1 Diabetes
CD	Celiak Disease
GFD	Gluten Free Diet
ND	Normal Diet
HbA1c	Hemoglobine A1c
IDAA1c	Insulin Dose Adjusted A1c
HLA	Human Leukocyte A insulin dose adjusted A1c
MMTT	Mixed Meal Tolerance Test
QoL	Quality of Life
B-glu	Blood glucose

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