DIABETES RESEARCH AND CLINICAL PRACTICE 120 (2016) 89–96

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

Continuous glucose monitoring and HbA1c in the evaluation of glucose metabolism in children at high risk for type 1 diabetes mellitus

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ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form
3 July 2016
Accepted 30 July 2016
Available online 6 August 2016

Keywords:
Type 1 diabetes mellitus
Autoantibodies
Glucose intolerance
Self-monitoring
Blood-glucose
Prediabetes

ABSTRACT

Aims: Continuous glucose monitoring (CGM) parameters, self-monitored blood glucose (SMBG), HbA1c and oral glucose tolerance test (OGTT) were studied during preclinical type 1 diabetes mellitus.

Methods: Ten asymptomatic children with multiple (⩾2) islet autoantibodies (cases) and 10 age and sex-matched autoantibody-negative controls from the Type 1 Diabetes Prediction and Prevention (DIPP) Study were invited to 7-day CGM with Dexcom G4 Platinum Sensor. HbA1c and two daily SMBG values (morning and evening) were analyzed. Five-point OGTTs were performed and carbohydrate intake was assessed by food records. The matched pairs were compared with the paired sample *t*-test.

Results: The cases showed higher mean values and higher variation in glucose levels during CGM compared to the controls. The time spent ⩾7.8 mmol/l was 5.8% in the cases compared to 0.4% in the controls ($p = 0.040$). Postprandial CGM values were similar except after the dinner (6.6 mmol/l in cases vs. 6.1 mmol/l in controls; $p = 0.023$). When analyzing the SMBG values higher mean level, higher evening levels, as well as higher variation were observed in the cases when compared to the controls. HbA1c was significantly higher in the cases [5.7% (39 mmol/mol) vs. 5.3% (34 mmol/mol); $p = 0.045$]. No differences were observed in glucose or C-peptide levels during OGTT. Daily carbohydrate intake was slightly higher in the cases (254.2 g vs. 217.7 g; $p = 0.034$).

Conclusions: Glucose levels measured by CGM and SMBG are useful indicators of dysglycemia during preclinical type 1 diabetes mellitus. Increased evening glucose values seem to be common in children with preclinical type 1 diabetes mellitus.

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http://dx.doi.org/10.1016/j.diabres.2016.07.027
0168-8227/

1. Introduction

Type 1 diabetes mellitus is a chronic autoimmune disease characterized by immune-mediated destruction of the pancreatic β-cells. The incidence of type 1 diabetes mellitus has been increasing worldwide, with the highest rate observed in Finland [1–3]. The preclinical phase of the disease can be identified through the presence of autoantibodies to pancreatic β-cell antigens [4]. Confirmed positivity for ⩾2 biochemical islet autoantibodies provide a cumulative risk of more than 80% during follow up for 15 years in children with HLA-conferred disease susceptibility [5,6].

The characteristics of glucose metabolism during the preclinical phase of type 1 diabetes mellitus have so far been monitored using oral and intravenous glucose tolerance tests (OGTT and IVGTT, respectively) which show deteriorating glucose tolerance and insulin secretion in high-risk children as the disease progresses [7–11]. It has been previously shown that HbA1c values start to rise as early as 2 years before the diagnosis of type 1 diabetes mellitus [12], and reported that HbA1c, OGTT and randomly measured plasma glucose values are useful in the prediction of the timing of the diagnosis in high-risk children [9,12,13].

Continuous glucose monitoring (CGM) is becoming more common in patients with clinical type 1 diabetes mellitus to monitor glycemic management. Regular CGM is associated with improved glucose levels, although the benefit seems to depend on target population [14,15]. In preclinical type 1 diabetes mellitus CGM might be helpful in the identification of individuals at high risk for progressing to overt disease in the near future [16–18]. Early identification of children with deteriorating glucose tolerance may prevent acute complications at clinical diagnosis. CGM could also be used to monitor glucose excursions in clinical trials aimed at secondary prevention of type 1 diabetes mellitus [19].

In this study the aim was to characterize the differences in glucose metabolism by using 7-day CGM combined with food records and calibration with self-monitored blood glucose (SMBG), HbA1c and five-point OGTT with glucose and C-peptide analyses in children with increased class II HLA associated genetic risk for type 1 diabetes mellitus and multiple (⩾2) biochemical islet autoantibodies in comparison with age- and sex-matched controls carrying a risk-conferring HLA class II genotype but testing negative for autoantibodies.

2. Methods

2.1. Study design

The Type 1 Diabetes Prediction and Prevention Study (DIPP) is a Finnish population-based cohort study in which genetically predisposed children are followed since birth for islet autoantibodies [20–22]. The current analysis included 10 children with preclinical type 1 diabetes mellitus (cases) defined as carrying HLA-conferred disease susceptibility and testing positive for at least two positive biochemical autoantibodies (insulin autoantibodies [IAA], GAD antibodies [GADA] or antibodies to the insulinoma-2 associated antigen [IA-2A]), and 10 age- and sex-matched control children with HLA-defined predisposition to type 1 diabetes mellitus but no autoantibodies. Autoantibodies were analyzed as previously described [6]. The age at seroconversion was defined as the age when at least one of the biochemical (IAA, GADA, IA-2A) islet autoantibodies was detected for the first time. The age at positivity for multiple autoantibodies was defined as the time point, when at least two biochemical islet autoantibodies were detected in the same sample. All CGMs were performed between March 2014 and February 2015. The study was approved by the Ethics Committee of the Oulu University Hospital, Oulu, Finland. All families participating in the study provided written informed consent.

2.2. Continuous glucose monitoring

Ten children with multiple biochemical islet autoantibodies were invited to continuous glucose monitoring with Dexcom G4 PLATINUM CGM (San Diego, CA) for one week. Age (±12 months) and sex-matched controls were also monitored for one week for paired comparison. When recruiting the study population the acceptance rate was 48% for case children and 36% for control children. CGM was started only in healthy children with no signs of acute infection. The use of the device was blinded during the study, so the participants were not able to see real-time CGM readings. The participants calibrated the device with self-monitored blood glucose values twice a day with a blood glucose meter according to the manufacturer's instructions. The families were asked to measure the child's SMBG every morning and evening with no special instructions related to meals. All the children were also invited to a five-point OGTT either at the beginning, or at the end of the CGM period. During the OGTT plasma glucose and C-peptide values were analyzed at 0, 30, 60, 90 and 120 min and a sample for HbA1c measurement was also taken. Body weight and height were measured and ISO-BMI was calculated for every participant at the beginning of the follow-up week [23]. The families were asked to keep food records during the seven days of CGM monitoring with precise timing of all meals and registration of all consumed nourishments. The study physician recruited the participants and installed the CGM device, and also gave guidance on the use of the Dexcom G4 Platinum glucose monitor, SMBG and food records. After the CGM period the physician reviewed the glucose results with the families.

2.3. Devices

All participants used the Dexcom G4 Platinum CGM equipment for which good accuracy and good patient experiences have been reported previously [24]. OGTT plasma glucose and C-peptide concentrations were measured in the Oulu University Hospital Laboratory. The hexokinase method was used for plasma glucose and a chemiluminescence method for C-peptide. HbA1c was analyzed with Advia 1800 (Siemens, Munich, Germany). SMBG was measured with the Bayer Contour glucometer (Bayer, Leverkusen, Germany) using the hexokinase based method.

2.4. Statistical analyses

The first 12 h of the CGM registration were discarded from the analyses to exclude possible false signals during the start of the monitoring. Primary variables given by the Dexcom device were the mean, minimum, maximum, standard deviation (SD), range of glucose values, time spent at or over a glucose value of 7.8 mmol/l, and time spent at or over 11.1 mmol/l. These cut-off values were chosen according to the WHO recommendations for impaired glucose tolerance and diabetes mellitus in an OGTT [25]. Glucose values at or over 7.8 mmol/l have been shown to be uncommon in healthy individuals [26]. Area under the curve (AUC) for the glucose values was calculated by the trapezoidal rule. The mean amplitude of glycemic excursion (MAGE) was calculated as previously described [27]. In addition, the postprandial glucose values (peak, mean, minimum, maximum, SD) were registered from the CGM data 2 h after each meal for the analyses. Day time was defined as between 6:00 am and midnight, and night time between midnight and 6:00 am. The daily amount of consumed carbohydrates was calculated from the list of consumed nutrients registered by the families (quality and quantity, time of intake) for every meal (breakfast, lunch, dinner and supper) during the study week. Snacks were also included in the total daily carbohydrates. Individual means of all tested parameters during the follow-up week were calculated and the statistical comparison was made with the paired sample *t*-test between the matched pairs. Spearman's rho was used to analyze the correlation between time since becoming positive for islet autoantibodies and markers of dysglycemia. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows (version 22.0; SPSS, Chicago, IL).

3. Results

3.1. Patient baseline characteristics

The baseline characteristics of the children with a risk-associated class II HLA genotype and multiple islet autoantibodies (cases) and their age- and sex-matched controls with class II HLA-conferred risk for type 1 diabetes mellitus but no autoantibodies are shown in Table 1. Baseline characteristics showed no significant differences between the case and control groups. All ten pairs completed the CGM-follow-up, seven pairs had measured HbA1c values, five pairs had OGTT results and eight pairs completed the food records.

3.2. CGM and SMBG values

The mean seven day CGM glucose level was higher in the cases, as were the day and night time CGM values (Table 2). The case children had also higher maximal CGM values and AUC for glucose. Higher variation in the CGM values was observed in the case children, with significant differences in the range ($p = 0.032$), standard deviation ($p = 0.040$) and MAGE ($p = 0.031$). The proportion of time spent at glucose levels $\geqslant$7.8 mmol/l was higher in the cases, 5.8% vs. 0.4%, (95% CI of the difference 0.3–10.4, $p = 0.040$), but no difference was observed for the time spent at glucose levels $\geqslant$11.1 mmol/l ($p = 0.152$).

When comparing the twice daily measured SMBG values the cases had higher mean glucose values in the evening ($p = 0.029$), higher maximum glucose values ($p = 0.038$) and higher glucose variability defined by the standard deviation of all SMBG values ($p = 0.020$); Table 2.

The clinically most relevant CGM and SMBG values are presented in Fig. 1.

Postprandial glucose values were also analyzed from the CGM data. The only significant difference in postprandial glucose values was observed in the peak glucose after dinner [6.6 mmol/l (SD 0.5) in the cases compared to 6.1 mmol/l (SD 0.4) in the controls; 95% CI of the difference 0.1 to 1.0, $p = 0.023$] (Table 2).

3.3. HbA1c and OGTT

The mean HbA1c was 5.7% (39 mmol/mol) in the cases and 5.3% (34 mmol/mol) in the controls. In paired comparison, the mean difference of HbA1c between the case and the control children was marginally statistically significant [95% CI of the difference 0.01–0.8% (0.1–9.0 mmol/mol); $p = 0.045$]. Plasma glucose values or serum C-peptide concentrations during the five-point OGTT showed no significant differences between the groups (Table 2).

Table 1 – Baseline characteristics of 10 age- and sex-matched children with increased class II HLA-associated genetic risk for type 1 diabetes mellitus and multiple biochemical islet auto-antibodies (cases) and 10 age- and sex-matched children with class II HLA-associated genetic risk but no autoantibodies (controls).

	Cases all	Controls all
Number of children	N = 10	N = 10
Mean age, years (SD)	9.8 (4.1)	9.9 (4.5)
Boys, n	7	7
Mean age at seroconversion, years (SD)	4.2 (3.2)	NA
Mean age at multiple ($\geqslant$2) autoantibodies, years (SD)	6.2 (3.9)	NA
ISO-BMI*, kg/m^2 (SD)	22.5 (3.8)	21.4 (3.0)
Mean duration of CGM, days (SD)	6.9 (0.3)	6.9 (1.2)
Mean number of SMBG values/day, *n* (SD)	2.3 (0.4)	2.0 (0.1)

* ISO-BMI is age and sex-adjusted body mass index reflecting the expected adult BMI [23].

Table 2 – Paired comparisons between the children with increased genetic risk for type 1 diabetes mellitus and at least two positive biochemical islet autoantibodies (cases) and their age- and sex-matched controls with genetic risk but no autoantibodies (controls).

CGM	*N*	Cases mean (SD)	Controls mean (SD)	95% CI of difference	*p*-value
Number of pairs	10				
7-Day CGM glucose, mmol/l		5.4 (0.6)	4.7 (0.3)	0.1 to 1.1	0.018
Day[1] CGM glucose, mmol/l		5.4 (0.5)	4.9 (0.4)	0.04 to 1.0	0.036
Night[2] CGM glucose, mmol/l		5.3 (1.0)	4.4 (0.4)	0.1 to 1.7	0.026
Maximum CGM glucose, mmol/l		9.1 (2.1)	7.1 (0.4)	0.4 to 3.5	0.018
Maximum day[1] CGM glucose, mmol/l		8.7 (1.8)	7.1 (0.4)	0.3 to 3.0	0.025
Maximum night[2] CGM glucose, mmol/l		7.0 (1.6)	5.4 (0.4)	0.3 to 2.9	0.020
Range of CGM glucose, mmol/l		5.7 (2.3)	3.9 (0.7)	0.2 to 3.5	0.032
Range of day[1] CGM glucose, mmol/l		5.3 (2.1)	3.8 (0.7)	0.1 to 3.1	0.043
Range of night[2] CGM glucose, mmol/l		2.8 (1.3)	1.7 (0.3)	0.2 to 2.0	0.025
7-Day CGM glucose values SD, mmol/l		1.2 (0.5)	0.8 (0.2)	0.02 to 0.7	0.040
Day[1] CGM glucose values SD, mmol/l		3.6 (1.4)	1.9 (0.4)	0.6 to 2.7	0.007
Night[2] CGM glucose values SD, mmol/l		0.7 (0.4)	0.4 (0.1)	0.1 to 0.6	0.020
CGM glucose, %Time $\geqslant$7.8 mmol/l		5.8 (7.0)	0.4 (0.4)	0.3 to 10.4	0.040
CGM glucose, %Time $\geqslant$11.1 mmol/l		0.8 (1.5)	0.0 (0.0)	−0.3 to 1.9	0.152
CGM glucose AUC, mmol/min/l		127.1 (13.2)	113.5 (7.1)	1.8 to 25.4	0.028
CGM glucose AUC day[1], mmol/min/l		96.2 (8.7)	88.0 (5.7)	0.6 to 15.9	0.038
CGM glucose AUC night[2], mmol/min/l		30.9 (5.6)	25.5 (3.1)	0.6 to 10.1	0.031
7-Day CGM glucose MAGE, mmol/l		1.2 (0.5)	0.8 (0.2)	0.04 to 7.5	0.031
SMBG, mmol/l					
Number of pairs	10				
7-Day SMBG glucose, mmol/l		5.3 (0.5)	5.0 (0.3)	−0.2 to 0.7	0.227
Morning[3] SMBG glucose, mmol/l		4.9 (0.6)	4.8 (0.4)	−0.6 to 0.6	0.899
Evening[3] SMBG glucose, mmol/l		5.8 (0.6)	5.3 (0.3)	0.1 to 1.0	0.029
Maximum SMBG glucose, mmol/l		8.1 (1.7)	6.6 (0.9)	0.1 to 2.9	0.038
7-Day SMBG glucose SD, mmol/l		1.3 (0.5)	0.8 (0.2)	0.1 to 0.8	0.020
HbA1c					
Number of pairs	7				
HbA1c%		5.7 (0.3)	5.3 (0.2)	0.01 to 0.8	0.045
HbA1c mmol/mol		39 (4)	34 (2)	0.1 to 9	
OGTT					
Number of pairs	5				
0-Min plasma glucose, mmol/		5.2 (0.3)	5.0 (0.1)	−0.2 to 0.6	0.266
30-Min plasma glucose, mmol/l		8.4 (1.6)	7.3 (0.9)	−0.8 to 3.0	0.190
60-Min plasma glucose, mmol/l		6.9 (2.7)	7.0 (2.0)	−5.1 to 4.7	0.923
90-Min plasma glucose, mmol/l		6.7 (1.3)	6.3 (1.7)	−2.6 to 3.6	0.702
120-Min plasma glucose, mmol/l		5.9 (1.1)	5.7 (1.3)	−1.2 to 1.4	0.814
OGTT plasma glucose AUC, mmol/min/l		27.5 (4.9)	26.0 (4.9)	−8.1 to 11.1	0.684
0-Min serum C-peptide, nmol/l		0.35 (0.12)	0.27 (0.11)	−0.08 to 0.23	0.246
30-Min serum C-peptide, nmol/l		1.17 (0.49)	1.09 (0.50)	−0.51 to 0.67	0.713
60-Min serum C-peptide, nmol/l		1.19 (0.49)	1.39 (0.74)	−0.69 to 0.30	0.329
90-Min serum C-peptide, nmol/l		1.30 (0.52)	1.49 (0.91)	−0.96 to 0.60	0.553
120-Min serum C-peptide, nmol/l		1.30 (0.57)	1.26 (0.71)	−0.36 to 0.45	0.768
OGTT serum C-peptide AUC, nmol/min/l		4.49 (1.77)	4.73 (2.47)	−1.92 to 1.45	0.719
Food records					
Meal specific carbohydrate amounts and postprandial CGM glucose values 60–120 min after the meal					
Number of pairs	8				
Breakfast					
Carbohydrates, g		38.7 (8.2)	41.0 (5.8)	−8.9 to 4.3	0.433
Mean postprandial CGM glucose, mmol/l		5.7 (1.1)	4.9 (0.3)	−0.3 to 1.7	0.122
Maximum postprandial CGM glucose, mmol/l		7.5 (2.0)	6.1 (0.4)	−0.3 to 3.2	0.086
Lunch					
Carbohydrates, g		49.6 (10.4)	52.0 (8.9)	−14.5 to 9.5	0.641
Mean postprandial CGM glucose, mmol/l		5.2 (0.6)	5.1 (0.3)	−0.4 to 0.8	0.539
Maximum postprandial CGM glucose, mmol/l		6.6 (1.0)	6.2 (0.5)	−0.7 to 1.5	0.444

Table 2 – (continued)

CGM	N	Cases mean (SD)	Controls mean (SD)	95% CI of difference	p-value
Dinner					
Carbohydrates, g		52.6 (15.2)	51.1 (11.7)	−8.5 to 11.4	0.741
Mean postprandial CGM glucose, mmol/l		5.5 (0.6)	5.2 (0.4)	−0.1 to 0.8	0.143
Maximum postprandial CGM glucose, mmol/l		6.6 (0.5)	6.1 (0.4)	0.1 to 1.0	0.023
Supper					
Carbohydrates, g		58.4 (31.8)	49.9 (17.3)	−16.4 to 33.6	0.445
Mean postprandial CGM glucose, mmol/l		5.7 (0.7)	5.2 (0.3)	−0.1 to 1.2	0.095
Maximum postprandial CGM glucose, mmol/l		7.1 (1.0)	6.3 (0.4)	−0.2 to 1.8	0.109
Total daily carbohydrates, g		254.2 (55.1)	217.7 (50.2)	3.6 to 69.5	0.034

The mean values with standard deviations (SD), differences of means with 95% confidence interval (95% CI) and p values of paired t-tests are presented for parameters from continuous glucose monitoring (CGM), self-monitored blood glucose values.
(SMBG) and HbA1c and variables from five-point oral glucose tolerance tests (OGTT). In addition, postprandial glucose values obtained from the CGM and food record data during the 7-day CGM are presented.
[1] Day time was defined as between 6:00 am and midnight.
[2] Night time was defined as between midnight and 6:00 am.
[3] The patients/families were instructed to take SMBG twice a day (morning and evening) with a blood glucose meter.

3.4. *The time since seroconversion and markers of dysglycemia*

We also analyzed possible correlations between the time since becoming positive for islet autoantibodies and various markers of dysglycemia (HbA1c, the mean CGM glucose, the mean AUC for CGM glucose, 7-day CGM glucose SD, MAGE, and the time spent ⩾7.8 mmol/l) but no correlations were found.

3.5. *Food records*

The amount of carbohydrates ingested showed no significant differences in any of the meals between the cases and controls, but the total amount of daily carbohydrates including snacks between the main meals was slightly higher in the cases [254.2 g (SD 55.1) compared to the controls, 217.7 g (SD 50.2); 95% CI of the difference 3.6–69.4; $p = 0.034$] (Table 2).

4. Discussion

This study demonstrates that asymptomatic children with preclinical type 1 diabetes mellitus defined by positivity for multiple biochemical islet autoantibodies have higher glucose levels and higher glycemic variation when monitored with CGM in comparison to autoantibody-negative controls. Especially, the evening glucose values detected by CGM and also by SMBG were higher in these children than in the controls.

In the CGM analysis the proportion of time spent at a glucose level at or over 7.8 mmol/l during the 7-day follow-up period was 5.8% in the islet autoantibody-positive children compared to only 0.4% in the autoantibody-negative controls. Recently, CGM data was also analyzed among autoantibody positive children ($n = 14$) and autoantibody negative controls ($n = 9$) in the DAISY Study [16]. According to their findings, autoantibody-positive children spent as much as 18% of their time at or over the cut-off value of 7.8 mmol/l [16] and autoantibody-negative control children with increased HLA-conferred risk also spent as much as 9% over the cut-off limit. Previously Fox et al. studied 74 healthy individuals without diabetes aged 9–65 years with CGM, showing that only 0.4% of the follow-up time was spent over the cut-off 7.8 mmol/l [26], which is exactly the same as seen in the control group in our study. According to our study the cut-off 7.8 mmol/l could be a more specific marker for detection of upcoming disease than previously reported by Steck et al. [16]. Our findings are further supported by the results of van Dalem et al. who also reported that increased time spent ⩾7.8 mmol/l during CGM may be useful in detecting early dysglycemia in preclinical type 1 diabetes mellitus [18].

To our knowledge this is the first study to report increased evening glucose concentrations in children with preclinical type 1 diabetes mellitus. Higher CGM values postprandially after dinner and higher SMBG values in the evening were observed (Table 2). This observation is in good accordance with the clinical experience showing that young children with established type 1 diabetes mellitus need higher basal insulin doses in the evening [28]. SMBG samples were obtained with no instructions related to meals, possibly interfering with pairwise comparison. The value of evening glucose measurements in the prediction of clinical diagnosis remains to be assessed further in more detail and in larger series of subjects with preclinical type 1 diabetes mellitus. OGTTs or mixed meal tolerance tests performed in the evening could show different results than the standard tests performed in the morning after overnight fasting. New studies are needed to explore this hypothesis.

Rather surprisingly, the postprandial CGM glucose values after breakfast and lunch were not different between our case and control children. This result is, however, in line with the lack of significant differences in plasma glucose values between the case and the control children during the OGTT. On the basis of these observations it seems that increased variation over 24 h and slightly elevated mean CGM glucose levels occur in the preclinical stage of type 1 diabetes mellitus before postprandial changes.

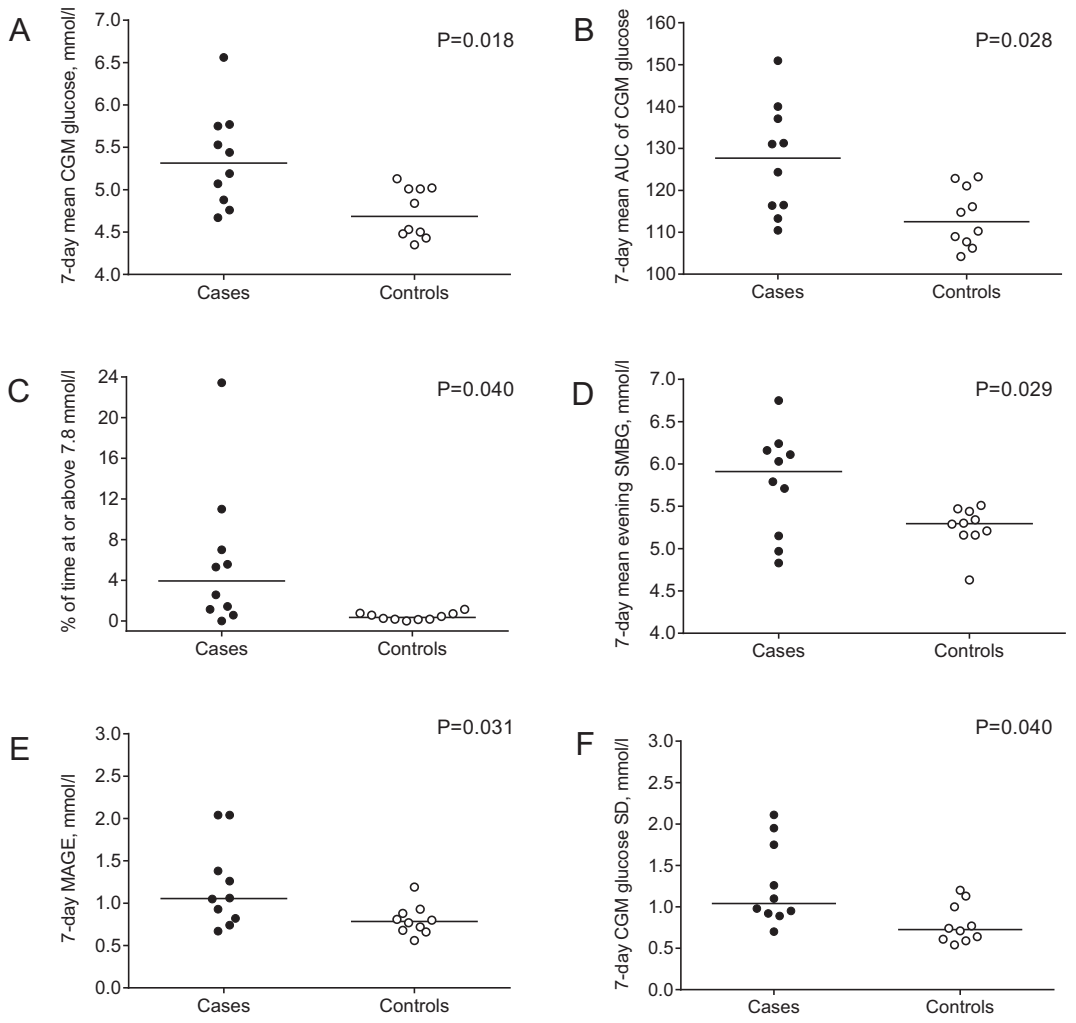

Fig. 1 – Dot-plot charts of clinically relevant differences in continuous glucose monitoring (CGM) and self-monitored blood glucose (SMBG) in asymptomatic children with multiple (⩾2) islet autoantibodies (cases) and age and sex-matched autoantibody-negative controls. The mean CGM glucose (A) and area under the curve (AUC, mmol/min/l, B) during the 7-day follow-up were significantly higher in the case group. The time spent at or above the cut-off glucose value of 7.8 mmol/l measured with CGM (C), and evening SMBG values (D) were higher in the cases. Increased variation in the CGM glucose values characterized by mean amplitude of glycemic excursion (MAGE, E) and overall standard deviation (SD) during 7-day CGM (F) was observed in the case children compared to the controls.

HbA1c values showed significant differences between the case and control children despite the small number of study subjects included in this series. The utility of monitoring HbA1c in the prediction of the timing of type 1 diabetes mellitus has been implicated by previous follow-up studies in children at risk for overt type 1 diabetes mellitus [12,29].

In the current small series plasma glucose concentrations in OGTT were not different between the case and control children. The use of OGTT in the prediction of type 1 diabetes mellitus has been widely studied, but the sensitivity of the test has proven rather disappointing [9,13]. Randomly taken plasma glucose has also been assessed in studies aimed at early recognition of type 1 diabetes mellitus with high specificity but with poor sensitivity [9]. In the current study SMBG values were higher when considering the mean and maximal concentrations, and also the variation in SMBG levels. The poor sensitivity previously reported was observed when glucose samples were taken every 3–6 months, and this could most likely be improved simply by increasing the number of SMBG measurements and shortening the intervals between the measurements. It could be feasible to obtain several daily SMBG values over a short period of time, e.g. during one week, and analyze the predictive characteristics of this data.

One shortcoming of the present study is that only five of the control children accepted to undergo an OGTT and seven to give a sample for HbA1c analysis. One child in each group completed the food record inadequately. Especially the OGTT parameters may be misleading due to the small study population. Families whose child refused to undergo the tests considered it too time consuming or inconvenient for the participant. There is wide variation in time from detection of autoantibodies to clinical type 1 diabetes mellitus and emergence of dysglycemia is a rather late phenomenon before diagnosis. It is possible that our OGTT series included

case children who still were at the early stage of preclinical diabetes mellitus and therefore no differences could be seen between our cases and the controls.

When analyzing the relationship between the time since becoming positive for islet autoantibodies and various markers of dysglycemia no significant correlations were found. It is difficult to draw firm conclusions because of the small sample size of our study. However, long-term follow-up of subjects with multiple islet autoantibodies have shown that clinical diabetes is diagnosed at a constant rate over long time periods [5]. Some subjects with persistent islet autoimmunity are rapid progressors and others may remain normoglycemic for years before progressing to diabetes. Thus it would be logical that the time from seroconversion does not necessarily correlate with the markers of dysglycemia.

Monitoring of glucose metabolism may be useful in the identification of emerging type 1 diabetes mellitus in high-risk children, as suggested previously [16–18], and may help the family to prepare for the diagnosis. It is important to note that early diagnosis of type 1 diabetes mellitus prevents diabetic ketoacidosis at disease onset and thereby reduces the burden for the patient and their family and shortens the initial hospitalization as well [30]. The overall prevalence of diabetic ketoacidosis among children with newly onset type 1 diabetes mellitus in Finland is approximately 20% [31], but significantly lower in children with prospective follow-up before the onset [30]. It is also possible that participation in preclinical follow-up studies and awareness of positivity for islet autoantibodies induces stress in the families of children with high risk for progression to type 1 diabetes mellitus, and in motivated subjects, CGM may provide further information about the glycemic status and relief when interpreted together with the study personnel. Furthermore, reliable tools are needed for monitoring glucose metabolism during the preclinical stage of type 1 diabetes mellitus in secondary prevention studies aimed at postponing or even preventing the disease by trying to preserve the endogenous insulin secretion [32].

In conclusion, these results show that CGM, HbA1c and evening SMBG measurements may be useful monitoring tools for emerging dysglycemia in children with preclinical type 1 diabetes mellitus.

Funding

This work was supported by the following grants. International: JDRF International (grants 4-1998-274, 4-1999-731, 4-2001-435); European Union (grant BMH4-CT98-3314); Novo Nordisk Foundation. Finland: Academy of Finland (Centre of Excellence in Molecular Systems Immunology and Physiology Research 2012-2017, Decision No. 250114); TEKES National Technology Agency of Finland; Special Research Funds for University Hospitals in Finland; Finnish Office for Health Technology Assessment; Diabetes Research Foundation, Finland; Sigrid Juselius Foundation; Emil Aaltonen Foundation; Jalmari and Rauha Ahokas Foundation; Signe and Ane Gyllenberg Foundation; the Research Foundation of Orion Corporation; Foundation for Pediatric Research; Alma and KA Snellman Foundation; Päivikki and Sakari Sohlberg Foundation and Finnish Cultural Foundation, North Ostrobothnia Regional Fund.

Duality of interest

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

Contribution statement

OH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. OH, JI, MK and RV contributed to the study concept and design. OH, JI, MK and RV contributed to the acquisition of the data. OH, TP, PT, MK and RV contributed to the analysis and interpretation of the data. OH, TP, PT, MK and RV drafted the manuscript. OH, TP, PT, JI, MK and RV critically revised the manuscript for important intellectual content. TP was responsible for the statistical analysis. OH, TP, PT, JI, MK and RV provided administrative, technical or material support. RV supervised the study. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors state no potential conflicts of interest.

Acknowledgements

We thank the dedicated personnel of the DIPP study in Oulu, Tampere and Turku; and the study children and their families for their essential contribution.

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