Project summary

Type 1 diabetes (T1D) is a chronic disease which requires daily calculations of food intake and insulin dose adjustment to achieve good glycaemic control and minimise the risk of developing diabetic complications. However, even when glycaemic control appears to be good, as demonstrated by average glycated haemoglobin (HbA1c), children and young people with T1D frequently experience glucose variability, with levels above and below the target range. The main cause of diurnal glucose variability is food intake, which can cause postprandial hyperglycaemia. Postprandial hyperglycemia can occur after any meal, although there is some evidence that it may be worse after breakfast. There is limited data on the occurrence and cause of this and its association with different variables, including food composition.

Methods:

This project will be a quantitative, descriptive study. It will aim to describe distribution and dispersion of both glucose variability and postprandial hyperglycaemia following breakfast. The study proposes to recruit approximately 435 children and young people who have T1D and who regularly use Dexcom continuous glucose monitoring (CGM). Recruitment will be via their managing dietitian. The dietitian will be asked to provide baseline information about the participants which will include demographic data and information on clinical data, treatment and anthropometrics. Participants will be asked to provide access to Dexcom CGM data throughout the period of recording. Participants will then be issued with, for seven consecutive days, two survey questionnaires, one in the morning at breakfast time and the other in the evening. The morning survey will include questions on the breakfast meal (including a photograph of the meal) and insulin dosage, similarly the evening survey will also include questions on diabetes management and food and fluid intake in addition to questions on activities all of which took place during the four-hour postprandial period. These data will be statistically described using univariate, bivariate and multivariate analysis.

Study protocol

Full Study Title:

An investigation into diurnal variability in glucose levels in paediatric patients with Type 1 Diabetes (T1D) and their responses to different food compositions.

Short title

Glucose variability in Type 1 Diabetes (T1D) and glycaemic responses to food composition.

Summary Protocol version number 4, date: 15/05/2021. IRAS ID: 273640. REC reference: 20/WS/0123

Chief Investigator:	Dr Stuart Galloway, University of Stirling, Stirling FK9 4LA s.d.r.galloway@stir.ac.uk. 01786 466494
Investigators:	Dr Ashley Shepherd, University of Stirling, Stirling FK9 4LA ashley.shepherd@stir.ac.uk 01786 466334
	Julie Johnson, University of Stirling and NHS Highland, julie.johnson1@stir.ac.uk, 07815893076
Statistician	Dr Federico Andreis, Health Sciences, University of Stirling, Stirling FK9 4LA. Federico.andreis@stir.ac.uk 01786 466252
Lead Sponsor:	Rachel Beaton, Research Integrity and Governance Manager, University of Stirling, Stirling FK9 4LA. Rachel.beaton@stir.ac.uk 01786 466196
Lead R&D	Frances Hines, Research, Development and Innovation Manager, NHS Highland, Centre for Health Sciences, Raigmore Hospital, Old Perth Road, Inverness, IV2 3UJ. frances.hines@nhs.scot. 01463 255822
Funder:	NHS Highland
Ethics approval:	This study has been reviewed and provided a favorable opinion by the NHS, Invasive or Clinical Research (NICR) Panel, University of Stirling and the West of Scotland Research Ethics Service (WoSRES) REC 5.

List of Contents

Rationale

Introduction

Type 1 diabetes (T1D) is caused by autoimmune destruction of the beta-cells that secrete insulin (Eisenbarth, 1986; Bluestone *et al.* 2010). It requires life-long treatment of insulin therapy, with the aim to achieve near-normoglycaemia, gauged by the amount of glycated haemoglobin, or HbA1c concentration, there is in the erythrocytes (Bunn *et al.* 1978). This measurement of HbA1c, against a clinically 'desired' target (DiMeglio *et al.* 2018), is a gold standard element of diabetes management (DCCT, 1993). Despite this, HbA1c, as a mean measurement, does not reflect the full pattern of glycaemia (Derr & Garrett, 2003) and cannot be used to foresee glucose variability (Boland *et al.* 2001). Even when HbA1c is in target, nocturnal and diurnal glucose variability, involving both hypo- and hyperglycaemia can be a daily occurrence for children and young people with T1D (Boland *et al.* 2001; Tansey *et al.* 2016). Data from continuous glucose monitoring (CGM) has shown that children experience nocturnal hypoglycaemia and diurnal hyperglycaemia, particularly postprandial hyperglycaemia (Boland *et al.* 2001; Tansey *et al.* 2016) and there is some evidence that this is worse after breakfast (Boland *et al.* 2001; Heptulla *et al.* 2004; Gandrud *et al.* 2007).

Complications

One of the reasons glucose variability and postprandial hyperglycaemia are a concern is that they both contribute to overall diabetes control (Standl *et al.* 2011). Poor glycaemic control causes cumulative and deleterious effects on both the cardiovascular (Koivisto *et al.* 1996) and microvascular systems (Kaiser *et al.* 1993). A further concern for children and young people, living with diabetes, is that they are vulnerable to alterations in glucose concentrations in the central nervous system owing to their high requirement for glucose for brain growth and development (Chugani *et al.* 1987). Several studies have observed alterations to both white and grey matter in children and adults with T1D (Perantie *et al.* 2007; Perantie *et al.* 2011; Marzelli *et al.* 2014; Mauras *et al.* 2015; Marziaka *et al.* 2016) and studies using CGM have observed an association with this and both glucose variability and hyperglycaemia (Marzelli *et al.* 2014; Barnea-Goraly *et al.* 2014; Mauras *et al.* 2015; Marziaka *et al.* 2016). Children with T1D often perform worse on cognition tests than those without the disease and decreases in IQ have been noted during periods of hyperglycaemia (Gonder-Frederick *et al.* (2009). T1D also appears to increase the risk of mental health difficulties (Butwicka *et al.* 2015) and this is associated with hyperglycaemia (McDonnell *et al.* 2007).

Possible solutions to postprandial hyperglycaemia

One potential solution to postprandial hyperglycaemia arises from the development of faster acting insulin. These could improve the lag time between insulin action and food absorption

(Bowering *et al.* 2017). Results of their ability to reduce postprandial hyperglycaemia are conflicting (Bode *et al.* 2017; Buse *et al.* 2018) and there are currently no published trials involving children and young people (Danne *et al.* 2018). One advantage of faster acting insulins is found in their potential use in closed-loop systems (CLS) (Gingras *et al.* 2018) which respond automatically to CGM readings (Gingras *et al.* 2018). Postprandial glucose control remains a challenge for the CLS and the time spent above target is mainly after food consumption (Gingras *et al.* 2018). The development of CLS has driven vast improvements in the accuracy of CGM systems in recent years and CGM is now better able to identify postprandial hyperglycaemia because of the density of data it affords (Tansey *et al.* 2016; Mangrola *et al.* 2017). CGM will likely help identify diverse responses to the myriad of dietary components (Bell *et al.* 2015) and thus CGM will likely allow for better prandial decision-making.

It is agreed that further research into the dietetic management of T1D is required (Smart *et al.* 2018). There is also a dearth of evidence on prevalence and management of postprandial hyperglycaemia after breakfast. Seven studies tested meals at breakfast time (Ryan *et al.* 2008; Smart *et al.* 2012; Smart *et al.* 2013; Piechowiak *et al.* 2017; Faber *et al.* 2017; Lopez *et al.* 2018) however none of the aims of these studies were to establish prevalence nor resolution of postprandial hyperglycaemia at breakfast. Only two considered diet quality at breakfast (Ryan *et al.* 2008; Groele *et al.* 2014) and neither of these provided any evidence of how to manage postprandial hyperglycaemia after breakfast.

Conclusion

It is known that chronic hyperglycaemia causes increased risk of diabetic complications. It is possible that both glucose variability and postprandial hyperglycaemia are independent risk factors for this as well. There is some evidence that glucose variability and postprandial hyperglycaemic are common occurrence for children who have T1D. However, there is a paucity of published data on the prevalence of postprandial hyperglycaemia after breakfast in children and young people with T1D and no evidence-base for how to manage this phenomenon. The need for long-term studies to examine glucose variability from CGM data and, for closer examination of postprandial glucose variability to elucidate methods to reduce this, has been highlighted (Tansey *et al.* 2016). Although this applies to all meals, focusing on minimising postprandial hyperglycaemia after breakfast is paramount. This can help ensure good control through the morning and rest of the day when children are at school and actively learning (Tansey *et al.* 2016).

Aim:

To describe the distribution and dispersion of glucose variability and postprandial hyperglycaemia following breakfast, in children and young people with type 1 diabetes (T1D), using measurements from Dexcom CGM.

Objectives:

- To determine the glucose variability diurnally and nocturnally and in the four-hour postprandial breakfast period using measurement of 'time in range', 'time above range' and 'time below range'.
- To determine the variability of glucose excursion, level and peak and the recovery time in the four-hour postprandial breakfast period.
- To determine the number and percentage of participants who achieved internationally agreed pre and postprandial glucose targets at breakfast time.
- To describe comparisons between all the above measurements and the variables of sex, age, disease duration, BMI, HbA1c, insulin dose/sensitivity and insulin regimen.
- To describe comparisons between all the above measurements and food compositions taken in the breakfast meal.
- To describe comparisons between the above measurements and carbohydrate and insulin adjustments, fluid intake and activities that took place during in the four-hour postprandial breakfast period.

Study design

This is a descriptive, quantitative study. Dexcom CGM data will be collected retrospectively (for the previous three months) and for the period of recording. Photographic food diaries and answers to morning and evening questionnaire surveys will be collected for seven consecutive days. The morning questionnaire will request information on food and fluids consumed at breakfast as well as insulin management. The evening questionnaire will request information on the four-hour postprandial morning activities in addition to insulin and carbohydrate adjustments and fluid intake. The study duration, commencing with the recruitment of the first participant and ending when data has been fully described, is anticipated to be eighteen months.

Participants

Eligibility criteria

- Children and young people aged between 1-17 years
- Diagnosis of type 1 diabetes for a minimum of one year

- Using multiple daily injections (MDI) together with carbohydrate counting or Continuous Subcutaneous Insulin Infusion (CSII)
- Using Dexcom continuous glucose monitoring (CGM) on a regular basis.
- Access to internet and email

Exclusion criteria

- Prescribed anti-hyperglycaemia agents *i.e.* Glucophage (Metformin) and or antidepressants.
- Have other medical conditions, including complications of diabetes and coeliac disease will be excluded.
- Currently enrolled in another research study

Recruitment

Paediatric diabetes dietitians, working across the UK, will be enrolled to help recruit participants and become principal investigators for their site. On enrolment, the researcher will provide the dietitians with all the relevant participant information sheets and consent forms as well as an Excel spreadsheet for entering the baseline information. The study documentation are presented in Appendices 1-13.

Sample size

There are approximately 29,000 children and young people living in the UK with T1D (Juvenile Diabetes Research Federation (JDRF), 2018). The numbers of patients using Dexcom CGM appears to be on average 11% of this population. The number of dietitians, working in paediatric diabetes, is typically 0.5 whole time equivalent per 100 patients (National Paediatric Diabetes Audit, 2019) resulting in approximately 180 paediatric diabetes dietitians working in the UK. Contact with dietitians, to date, suggests it may be possible to gain agreement from approximately 18% of dietitians who are contacted directly. These dietitians would be managing an estimated 5220 patients. Assuming 11% of these use Dexcom CGM then an approximate number of participants that could be recruited is 572 resulting in approximately 18 participants per dietitian. An average of 13-14 participants per dietitian would keep the workload to an average of no more than two working days. The time required for the researcher to contact participants, download and analysis data and food diaries is estimated to be 90 – 120 minutes per participant. For 435 participants this is the equivalent of 75-100 working days which is achievable.

Methodology

Baseline data

In order to make comparisons between relevant variables and glucose levels, the following baseline data will be collected from the dietitians and sent to the researcher, along with the artificial identifier on the Excel spreadsheet as discussed earlier at the stage of recruitment of participants:

- Parent's email address
- Sex, date of birth and recent weight and height (for calculation of BMI and BMI centile)
- Date of diagnosis of T1D
- Last four HbA1c
- Total daily insulin dose (TDD)
- Percentage basal/bolus (if known)
- Insulin: carbohydrate ratios (ICR) and Insulin Sensitivity Factor (ISF)
- Current insulin regimen (including type of insulin prescribed and if applicable type of insulin pump i.e. open or closed loop)

Glucose measurement

Data on interstitial glucose will be collected via Dexcom CGM. The Dexcom CGM data will be accessed by registering a research 'Clarity Clinic' with Dexcom CLARITY® Clinic Portal (Dexcom In, San Diego, CA, USA) with the researcher becoming the administrator of this clinic. Once the managing dietitian has obtained each participant's consent, the participant's parent's email address will be sent to the researcher along with the baseline information/data as described above. The researcher, as administrator of the Clarity Clinic account, will then invite the participant, via email, to be added to the clinic. Once the invite has been accepted, it will stand for the period of the recording i.e. until the participant's questionnaires been received unless the participant decides to withdraw from the study. Once the participant has submitted their last questionnaire, they will be removed from the Dexcom CLARITY® Clinic Portal.

Survey questionnaires and photographic food diaries

Following the provision of CGM data, participants will be asked to complete the questionnaires using 'online survey'. Participants will be asked to photograph their breakfast meal and drinks and email along with provide information after breakfast and in the evening, as per the questionnaire presented in Appendix 14 and 15. The CGM data will be collected throughout this time as discussed above.

The food consumed at breakfast will be analysed using Diet Plan 7, a nutrient analysis programme based on the UK food composition tables (Public Health England, 2014). This will provide a calculation of energy and macro and micronutrient intake and allow the accuracy of carbohydrate calculations to be assessed. Where possible, the glycaemic index of the breakfast will be calculated. The analysis from this will be transferred into a CSV file and saved as an Excel spreadsheet as presented in Appendix 16.

Recruitment for Dexcom CGM DATA only

As per Amendment 273640.10, dated 15/05/2021, participants can be recruited to provide CGM data only. This amendment as submitted in order to attempt to obtain large quantities of CGM data as recruitment to the study has been slow. Some families have reported to the recruiting dietitians (Principal Investigators) that they have been reluctant to join because of the time commitment required for completing the survey questionnaires.

Outcome measures

Primary and secondary outcome measures will be based on international guidelines and consensus DiMegloi *et al.* 2018; Battelino *et al*. 2019) of the metrics and target glucose levels to be used in CGM analysis in clinical practice. These are agreed to be:

Metrics:

- Mean glucose
- Glucose variability (GV) % coefficient of variation (COV) target ≤36%
- Time in range (TIR) % and time spent between 3.9-10mmol/l
- Time above target (TAR) % and time spent >10.1-<13.9mmol/l) and >13.9mmol/l
- Time below range (TBR) % and time spent 3.0-3.8mmol/l and <3mmol/l

Target glucose levels:

- TIR - % of readings >70% or 16hr 48min
- TAR - % of readings <25% or <6hr high and <5% 1hr 12min very high
- TBR- % of readings <4% or <1hr low and <1% or <15min very low

Primary outcome measure:

- Mean glucose (mmol/l) in the four-hour postprandial breakfast period calculated from the CGM measurements at 5 minutes intervals.

Secondary outcome measures – post prandial period:

- Number and percentage who had pre-prandial glucose in target Mean peak glucose level (mmol/l), mean time to peak (mins), mean time to recover (to pre-prandial levels) (mins) in the four-hour postprandial breakfast period

- TIR, TBR and TAR (% and time) in the four-hour postprandial breakfast period
- Comparisons of the above measurements between cohorts and breakfast meal compositions and drinks, snacks taken in the morning and activities and insulin adjustments taken in the 4-hour postprandial period.

Secondary outcome measures – glucose variability:

- TIR, TBR and TAR (% and time) between the hours of 06.00-22.00, 22.00-06.00 and 24-hour period.

Data analysis

This will be a mix of univariate, bivariate and multivariate analysis as this is best suited to describing, summarising and visualising these data. Outputs will include the distribution of glucose levels and diurnal, nocturnal and post-breakfast variability to determine the spread and dispersion of the data. As well as providing new evidence on this phenomenon, it will also assist in determining required sample size for any subsequent investigation including an intervention testing of effects on interstitial glucose levels arising from different food intakes.

Safety considerations

Recruitment/consent

Consideration will be given to those potential participants/families who are experiencing difficulties managing their condition, for example 'diabetes burnout'; poor glycaemic control or other stressors, for example, family difficulties, stress at school, for example, dealing with bullying or exam pressures. This will be minimised by recruiting via the managing dietitian who will have significant knowledge of the potential participant and who will be expected to discourage recruitment, if it is felt the family have enough to cope with. Those who are newly diagnosed will not meet the eligibility criteria as it is felt this would be unethical given the pressure they will be experiencing dealing with a new diagnosis of a chronic disease. Participants will not be asked to change their usual diabetes management or dietary intake.

Personal data collection

Personal data as described above will be collected and will be securely managed. How this will be managed is described in the 'Data Management' section.

Burden on dietitians

Dietitians, as Principal Investigators, will need to be allowed additional time to recruit participants. Dietitians will be asked to discuss this with their managers and gain their approval for this and also with their diabetes teams.

Burden on families

This is minimised by utilisation of digital technology to ensure that completion of food diaries and questionnaire surveys are not time consuming. Payment for expenses and time may be considered. Funding to support this (from the British Dietetic Association) will be applied for but can only be submitted once ethical approval has been sought and granted.

Data management

Assessment of existing data

There appears to be a dearth of available data on the distribution and dispersal of glucose levels in children and young people who have T1D. Nor does there appear to be any published data comparing glucose measurements from Dexcom CGM with different breakfast compositions in children and young people with T1D. The project is therefore not creating new data when existing data could be re-used.

Creation of new data

This will include the following:

- Retrospective and on-going Dexcom CGM measurements of interstitial glucose
- Baseline information as discussed earlier
- Information and analysis of food and drink intake at breakfast and activities and adjustments in the four-hour postprandial period as discussed earlier.

Methods of anonymisation, pseudonymisation and encryption

None of participants names and addresses will be collected. Surnames are likely to be known, owing to the need to obtain email address for the CGM data collection. The participants date of birth is required for the Dexcom Clarity clinic. Pseudonymisation will take place as recommended by GDPR regulation (General Data Protection Regulation (GDPR) 2018). Artificial identifiers, to be used for all communication and data storage, will be provided for each participant at the stage of recruitment. All data, including parent's email addresses, will be stored on an NHS Highland secure remote server which is password protected with files encrypted. Breeches of data will be reported through both the Data Management Committee (see below) and the NHS Highland incident reporting system (DATIX).

Collection, storage and transfer of data - baseline information

Baseline information will be collected by the participant's managing dietitians, taken from diabetes clinical records. These data will be pseudonymised with the artificial identifier and entered into an Excel spreadsheet, by the enrolled dietitian and communicated via 'NHS mail' (see Appendix 1). 'NHS mail' is accredited to government official status for sharing patient

identifiable and sensitive information and meets the secure email standard (DCB1596). All data will be stored on the NHS Highland laptop.

Collection, storage and transfer of data - Dexcom CGM data

The researcher will set up a research clinic on Dexcom CGM Clarity which is accessed via the internet and is password and username protected. The researcher, as administrator of this clinic, will then invite the participants, via their parent's email address, to join the clinic. This a standard way of accessing Dexcom CGM data. The invite will include the artificial identifier, and this is the identifier that will be visible when the data is accessed and not the name of the participant. For the invite to work it must include the participant's date of birth for verification purposes. Email addresses and date of birth will be recorded in the baseline information spreadsheet and this will be stored on the NHS Highland laptop. Dexcom have their own security management and personal information is transmitted in encrypted form. CGM data will transferred to a CSV file, saved as an Excel file and stored on an NHS Highland laptop. An example of this in presented in Appendix 17. As consumers of Dexcom CGM the participants will have access to the Dexcom, Inc Privacy Policy which complies with the GDPR) 2016.
(https://www.dexcom.com/en-GB/linked/documentservice/PrivacyPolicy).

Collection, storage and transfer of data - survey questionnaires

The researcher plans to use Jisc 'Online Surveys' (formerly BOS). The University of Stirling subscribes to this service and the researcher has a unique username and password for accessing this, known only to the researcher. Jisc is registered with the Information Commissioners Office (ICO) (registration number Z9546606) and meets the requirements of GDPR (https://www.onlinesurveys.ac.uk/gdpr-and-online-surveys/) and is certified to ISO 27001 (https://www.jisc.ac.uk/about/certification). All survey responses are collected over encrypted SSL (TLS) connections and deleted after three months. The university GDPR statement is added to all the survey questionnaires. Responses to the survey will be transferred to a CSV file then saved as an Excel file on the NHS Highland laptop. An example of this is presented in Appendix 18 and 19.

Collection, storage and transfer of data - Photo food diaries

The participants will be asked to only photograph the meal and not include anything else that may be identifiable in the photograph. Instruction on how to do this is provided in a separate sheet as presented in Appendix 20. The photographs will be emailed to the researchers NHS mail email account. These will be downloaded and saved to the NHS Highland remote secure

server as described above. Should any identifying information be included in the photograph this will be deleted from the photograph before it is saved.

Collection, storage and transfer of data - Nutritional analysis

The breakfast meals will be analysed using DietPlan 7 which will be accessed via an NHS Highland desktop. Data entered will be pseudonymised, using the artificial identifier as described below. The analysis will be transferred to a CSV file, saved as an Excel file and emailed via NHS mail to be saved on the NHS Highland laptop.

Data ownership

It is anticipated that new data, arising from the study, and the associated intellectual property will be owned jointly by the University of Stirling and NHS Highland with a sharing agreement. Dexcom were contacted about this, via email, in January 2020 and have failed to respond.

Destruction of data

The Dexcom Clarity clinic only stores CGM data for three months. Once these data have been collected for the period of the study, the Dexcom research clinic will be closed. Any transferred data will be stored on the NHS Highland secure remote server for 10 years before being deleted. Responses to surveys are backed up on the Online Survey system for three months then they are deleted and destroyed.

Reviewing the data management plan

At the suggestion of the NHS Highland Research and Development office, a Data Management Committee will be set up. Meetings will be arranged at regular intervals to ensure the data management plan is adhered to and to address any difficulties.

Expected outcomes

The aim of this study is to describe the distribution and dispersion of glucose variability and postprandial hyperglycaemia after breakfast and establish comparisons of these between variables obtained from baseline information and nutrient analysis. It is hoped this will formulate a quantitative research question and power calculation for a sample size for a intervention trial to test different meals at breakfast.

Dissemination of results

It is anticipated that one paper will be submitted for publication. The proposed journals for publication include:

- *Pediatric Diabetes*
- *Diabetic Medicine*

- *Diabetologia*
- *Diabetes Technology & Therapeutics*
- *Acta Diabetologica*.

Ethical considerations

This study has been reviewed and provided a favorable opinion by the NHS, Invasive or Clinical Research (NICR) Panel, University of Stirling and the West of Scotland Research Ethics Service (WoSRES) REC 5. Consent will be obtained from parents and/or carers and, where appropriate, the children and young people themselves. As Principal Investigators, the recruiting dietitians will be asked to encourage, where possible, the children and young people to be involved in the decision to participant in the study. To assist with this, several age appropriate 'Patient Information Sheets' have been developed and will be provided to the enrolled dietitians. The dietitians will therefore be asked to ensure conversations regarding the study be discussed when the child/young person is present. It should be noted that in Scotland, children over the age of 12 years old are usually considered to be mature enough to give a view about taking part in research even if they are not fully able to give consent. The recruiting dietitians will be asked to discourage parents from consenting to participate if their child expresses either verbally or non-verbally that they do not wish to participate.

Budget

Only participants already self-funding or receiving NHS funding for Dexcom CGM will be recruited therefore there will no cost for using Dexcom CGM. The University of Stirling already subscribe to www.onlinesurveys.ac.uk. Funding to purchase an NHS Highland laptop will be sought. Funding to pay expenses to participants and dietitians will be considered (applications to obtain financial support for this can only be submitted once ethical approval has been obtained).

Insurance

The University of Stirling provide indemnity insurance although the risk of adverse events is low given that this is a descriptive study.

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