Investigating the prodrome of type 1 diabetes in childhood as it presents to Primary Care to predict earlier diagnosis and reduce ketoacidosis at presentation, using pseudoanonymised linked Primary and Secondary Care data.

Sponsor:	Cardiff University 30-36 Newport Rd Cardiff CF24 0DE United Kingdom
Sponsor ref:	**SPON 1470-15**
Funder:	Novo Nordisk UK Research Foundation
Funder ref: None provided	
REC ref: 15/LO/2054	

This protocol has been authorised by:

Dr Mike Robling	SEWTU Director	MD	12.2.18
Name	**Role**	**Signature**	**Date**
Julia Townson	Chief Investigator	J. Townson	12.2.18.
Name	**Role:**	**Signature**	**Date**

General Information This protocol describes the Investigating the prodrome of type 1 diabetes in childhood presenting in Primary Care study and provides information about the procedures for acquiring/cleaning and analysing the data. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will

be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to SEWTU.

Compliance This study will adhere to the conditions and principles outlined in the EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding This study is being funded by the Novo Nordisk UK Research Foundation.

Contact details – Chief Investigator

CHIEF INVESTIGATOR

Julia Townson

Research Fellow

7th Floor, Neuadd Meirionnydd

Heath Park

Cardiff University

CF14 4YS

Tel : 02920 687606

Fax : 02920 687611

E-mail : townson@cf.ac.uk

CO-INVESTIGATOR(S)

Professor John Gregory

Professor in Paediatric Endocrinology & Honorary Consultant

Institute of Molecular &

Experimental Medicine

Wales School of Medicine

Children's Centre

Heath Park, Cardiff

CF14 4XN

Tel : 02920 742274

Fax : 02920 745438

E-mail : gregoryjw@cardiff.ac.uk

Professor Lesley Lowes

Florence Nightingale Foundation Chair of Clinical Nursing Practice Research

Cardiff University/Cardiff and Vale University Health Board

School of Healthcare Sciences

Room 12.08, 12th Floor, Eastgate House

35-43 Newport Road, Cardiff CF24 0AB

Eastgate House: 02920 688602

Mobile: 07971 643369

Cardiff and Vale UHB

Room 1.7, 1st Floor Ty Dewi Sant

University Hospital of Wales, Heath Park, Cardiff
CF14 4XN

Ty Dewi Sant: 029 20687534

Dr Nick Francis
Reader, Institute of Primary Care and Public Health

School of Medicine

Cardiff University

5th Floor, Neuadd Meirionnydd

Heath Park

Cardiff

CF14 4YS

Tel: +44 (0)29 20687133

Fax: +44 (0)29 20687219

E-mail: francisna@cf.ac.uk

Web: www.nick-francis.co.uk

Dr Rebecca Cannings-John

Research Fellow in Statistics

Institute of Primary Care and Public Health

Cardiff University

4th Floor, Neuadd Meirionnydd

Heath Park

Cardiff, CF14 4YS

Tel: +44(0)29 20687248

Email: canningsrl@cardiff.ac.uk

Dr Daniel Thayer

Senior Research Analyst

College of Medicine

Grove Building
Swansea University
Singleton Park
Swansea
SA2 8PP

Tel: 01792 602766

Email: d.s.thayer@swansea.ac.uk

Contact Details – Trial/Study Team:

STUDY MANAGER

Ms Julia Townson

Research Fellow

7th Floor, Neuadd Meirionnydd

Heath Park

Cardiff University

CF14 4YS

Tel : 02920 687606

Fax : 02920 687611

Email: townson@cf.ac.uk

Please contact the Study Manager for any queries

Table of Contents

Glossary of abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
CU	Cardiff University
DKA	Diabetic Ketoacidosis
EUCTD	European Union Clinical Trials Directive
ICH	International Conference on Harmonization
GCP	Good Clinical Practice
GP	General Practitioner
IC	Informed consent
HB	Health Board
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NISCHR	National Institute for Social Care & Health Research
PCT	Primary Care Trust
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAIL DATABANK	Secure Anonymised Information Linkage Databank
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
T1D	Type 1 Diabetes
TMF	Trial Master File
TMG	Trial Management Group

1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

2 Synopsis

Short title	Investigating the pathway of type 1 diabetes in childhood presenting in Primary Care
Acronym	
Internal ref. no.	
Study design	Case control study using the SAIL databank and the Brecon group database
Study participants	No direct participation with individuals
Planned sample size	Approx 400
Follow-up duration	Not applicable
Planned study period	November 2015 – October 2016
Primary objective	To investigate if there are any factors which may facilitate an opportunity for earlier diagnosis in Primary Care of children with type 1 diabetes
Secondary objectives	To investigate the risks of presenting in diabetic ketoacidosis (DKA)
Primary endpoint	Not applicable
Secondary endpoints	Not applicable
Interventions	Not applicable

3 Study summary

The aim of the research is to get a better understanding of the pathway to diagnosis of type 1 diabetes (T1D) in childhood. By exploring the number and reason for children's appointments with their GP, prior to being diagnosed with T1D, we may be able to develop ways to aid earlier diagnosis which ultimately will help to reduce the number of children who are seriously unwell with diabetic ketoacidosis (DKA) at diagnosis. DKA is a life threatening condition and the most common cause of hospitalisation and death in children with T1D. Sadly, children continue to die at presentation of T1D including in South Wales, 2 within last four years. DKA also causes significant illness with impacts on financial and medical resources. It has also been shown that children who do not present in DKA at diagnosis are less likely to have long term diabetes-related complications. Currently, the rate of DKA is unacceptably high in the UK.

Current literature suggests that there is a missed window for diagnosis and that 25% of children are still becoming very unwell, in DKA, at onset of T1D. Studies have found that almost 30% of newly diagnosed children had at least one visit with a medical practitioner prior to diagnosis and almost half had a delayed referral to secondary care. Risk factors for presenting in DKA at onset include delayed diagnosis. This study will build on these findings by undertaking an evaluation of the number of appointments, symptoms and diagnostic tests prior to diagnosis of approximately 400 children with T1D. By modelling these data with a cohort of matched children without T1D, it will be possible to ascertain any significant differences between the two cohorts and potentially identify strategies for earlier diagnoses and prevention of DKA.

Children diagnosed with T1D between 1st January 2000 and 31st December 2015 will be identified from the Brecon Group register. These data will be linked with the SAIL Databank. The SAIL analyst will anonymise the data so that no child can be identified e.g. date of birth will be removed and replaced with age at diagnosis. The SAIL analyst will also provide data from a group of children without T1D, at the ratio of 3:1, matched by age, gender and GP practice. The SAIL analyst will extract details of all of the visits that these children made to their GP over the previous 12 months. Therefore, the data will consist of a series of codes for symptom details, diagnoses, medications, tests undertaken and other illnesses or conditions. An exploration of any differences in GP consultations between those children who were in DKA at diagnosis and those who were not will also be undertaken.

4 Introduction

• Background

What triggers the onset of childhood T1D is still unknown but each year in the United Kingdom (UK) approximately 26 per 100,000 children will be diagnosed with the condition (1). Although the rate of diagnosis is reported to be rising by approximately 4% per year (2), it remains a relatively rare condition in primary care. A GP, working in a large practice, might expect to see a child with new onset T1D approximately once every two years (3). Identifying the condition has been described as 'looking for the needle in the haystack' (4) due to the non-specific nature of the clinical characteristics that can often be attributed to more common childhood conditions.

Recognition of the early symptoms of T1D is critical to ensure prompt treatment in order to avoid a child presenting in DKA, a potentially life threatening condition and the most common cause of hospitalisation and death in children with T1D (5). Sadly, children continue to die at presentation of T1D including in our own region (6). DKA also causes significant morbidity with impacts on financial and medical resources (7, 8). Children who do not present in DKA at diagnosis have significantly better residual beta cell function, resulting in improved glycaemic control and a higher rate of partial remission (9) with likely longer term reductions in diabetes-related complications, so-called 'metabolic memory' (10). Currently, the rate of DKA is unacceptably high in the UK (11).

In an effort to reduce the number of children presenting in DKA at diagnosis, various educational campaigns have been carried out around the world. By increasing awareness of the symptoms of T1D through the use of posters placed in schools and health centres; the provision of capillary blood glucose meters to doctors; and visits by educators experienced in diabetes management, the rate of DKA was reported to have reduced by 64% (12) and fell from 78% to 12.5% (13). However, in Wales, a poster campaign targeting pharmacies, GP surgeries and schools did not impact on rates of DKA at diagnosis, which remained static at 25% in the year following the campaign (14).

Gaining a greater understanding of the prodrome in the months before diagnosis could provide important information to assist development of prevention strategies to reduce the rate of DKA in the future. In a systematic review, Usher-Smith (2011) found that a considerable number of children have a delayed diagnosis or are misdiagnosed and that on average children were symptomatic for over two weeks before diagnosis (15). There is some suggestion that this may be an underestimate and children can exhibit subtle symptoms for over a month before they are diagnosed (4). Early detection may be hindered due to the child appearing relatively well, presenting with non-specific symptoms or because health practitioners have "missed" opportunities to make a diagnosis (4). One in three newly diagnosed children will have been seen by a healthcare professional at least once within the preceding weeks of their diagnosis (3).

In a qualitative study, Usher-Smith explored the pathway to diagnosis with families and GPs and identified that the greatest delay to diagnosis in the appraisal interval was attributable to parents (4). Most children in this relatively small study were diagnosed at their first GP encounter but in most cases, parents had already made or suspected the diagnosis themselves. However, the small sample size and retrospective recall of events limit interpretation of these results.

By investigating a large cohort of children, a more detailed understanding of the typical pathway to diagnosis can be formed including identification of opportunities for an earlier diagnosis. This study will link the Brecon Group Register, which contains diagnostic details including date of presentation of 98% of all known cases of T1D in Wales, with GP records held within the Secure Anonymised Information Linkage (SAIL) Databank. SAIL holds extensive Welsh population data, including primary,

secondary and social care data. It provides detailed clinical and demographic anonymised information on patients, including symptoms, diagnoses, prescriptions and medical history. This wealth of data makes it easier and more cost-effective to study much larger numbers of individuals over longer periods of time than is possible using traditional methods using prospectively collected data that are uninfluenced by recall bias. By analysing patients' consultations, recorded in SAIL, over the 12 months before diagnosis of T1D, a more detailed account of the prodrome of T1D in childhood will be developed.

This will be the first large scale study of the pathway to diagnosis in primary care, giving an unprecedented detailed account of the symptoms, numbers of visits, diagnostic tests, misdiagnosis and overall presentation of children with new onset T1D. Results will also build on research (the EDDY study: Early Diagnosis of Diabetes in Youth) currently being undertaken by the applicant and two of the co-applicants funded through the National Institute for Social Care and Health Research for Patient and Public Benefit scheme. EDDY is a feasibility study designed around King's (12) successful intervention in Australia, with the aim of designing and delivering interventions for parents, GPs and practice nurses, to raise awareness of the symptoms of T1D to prevent presentation in DKA at diagnosis. This study will identify whether there are additional opportunities to promote an earlier diagnosis, which may require interventions different or additional to those undergoing preliminary evaluation in EDDY.

• Research questions

1. Are there factors (number and reasons for consultations, socio-demographic factors, past medical history), or combinations of factors, that are associated with a new diagnosis of T1D, as compared to children presenting with other acute conditions in the 12 months before diagnosis?
2. Are there differences in the patient pathway (12 month period before diagnosis), as recorded in their medical records, between patients presenting with newly diagnosed T1D who experience DKA, and those who do not experience DKA around the time of diagnosis?

5 Study objective(s)

The ultimate aim of this research is to promote earlier diagnosis of type 1 diabetes (T1D) in childhood to reduce the risk of DKA at presentation by better understanding the pathway to diagnosis through analysis of the number and reason for appointments of the child with their Primary Care Team before diagnosis and any tests conducted at these times.

• Primary objective

- To investigate if there are any factors that are associated with a new diagnosis of T1D in childhood, compared to a matched group of controls without T1D, during the 12 months preceding diagnosis.

- **Secondary objectives**

- To investigate if there are any risks associated within the patient pathway in the 12 months preceding diagnosis between children who presented in DKA or not in DKA at diagnosis.

6 Study design

This is a case control study of a linked dataset (SAIL databank and Brecon Group database). Data from all children (15yrs and below) diagnosed with type 1 diabetes between 1st January 2000 to 31st December 2015 will be linked with the SAIL databank.

An anonymised data set will be created by the SAIL research analyst. This will include a cohort of matched controls who do not have T1D identified through the SAIL databank at a ratio of 3:1. The resulting dataset will contain all GP consultation records in the 12 months prior to diagnosis for children diagnosed with T1D, those diagnosed in DKA and a matched cohort of children without T1D.

Initial analysis of the dataset will use data mining techniques to assess and explore the read codes attached to each GP consultation. Further analyses will assess each patient's prodrome (12 months prior to diagnosis) by analysing the number of GP visits, symptoms, duration of symptoms, tests undertaken and treatments given.

7 Centre and Investigator selection

Not applicable

8 Participant selection

The first stage of the study will involve identifying all children (i.e. those under 15yrs of age) diagnosed with T1D from 1st January 2000 to 31st December 2015 in the Brecon Group Register and categorising

them into those who presented with or without DKA at diagnosis. Extrapolations from the Welsh data suggest that there will be approximately 3500 children diagnosed with T1D in these years, with at least 90 children who presented in DKA. The SAIL research analyst will link these data with the GP dataset from the SAIL databank using first and last name, gender, date of birth, date of diagnosis, DKA status, GP and postcode (NHS number is not recorded in the Brecon Group Register). The dataset generated from this process will be anonymised using an ALF, ensuring the researchers do not have access to any personal identifiable data (e.g. age at diagnosis in DKA will be calculated using date of birth and date of diagnosis and then date of birth will be discarded). In addition, a cohort of controls presenting to their GP with acute illness but who do not have T1D will be identified from SAIL at the ratio of 3:1. This cohort will be matched to the T1D cohort by age, gender and GP practice. The resulting dataset therefore will contain all GP consultation records in the 12 months prior to diagnosis for children diagnosed with T1D, those diagnosed in DKA and a matched cohort of children without T1D. The cohort of children without T1D will be assigned a matched date to act as the time point for consultations in the previous 12 months. Children presenting with T1D (in or not in DKA at diagnosis) who cannot be matched (due to their GP data not being available in SAIL) will be compared to children presenting with T1D matched to SAIL, and any differences will be quantified.

- **Inclusion criteria**

  - All children 15yrs and under diagnosed with T1D between 1st January 2000 and 31st December 2015 and listed in the Brecon Group database.
  - Matched controls, for those above, from the SAIL databank

- **Exclusion criteria**

- All children over 15yrs old diagnosed with T1D

- All children diagnosed before 1st January 2000 and after 31st December 2015

9 Outcome measures

There are no primary or secondary end points for this study

10 Recruitment

This study is using routinely collected data and therefore will not be actively recruiting participants

- **Informed consent**
  Informed consent will not be sought from participants as all data is anonymised and is provided from existing datasets.

- **Randomisation/registration and unblinding**

  This is a case control study and therefore no participants will be randomised.

- **Screening logs**

Not applicable

11 Withdrawal & loss to follow-up

Not applicable

12 Intervention

- Not applicable

13 Adverse Events

Adverse Event (AE):

There are no expected AEs/SAEs.

Related Adverse Event/Serious Adverse Events:

There are no expected AEs/SAEs that could be related to the study. Therefore, there will be no formal process in place to collect AEs or SAEs for this study.

Adverse Event (AE):

Not applicable

- **Causality**

Not applicable

- **Reporting procedures**

Not applicable

14 Study procedures

This study will link two existing datasets, the Brecon Group (Welsh Paediatric Diabetes Interest Group) Register and GP records within the SAIL databank, to provide a unique and contemporary dataset of all children in Wales diagnosed with T1D in the 16 year period between 1st January 2000 and 31st December 2015 (approximately 3500), with details of the number and nature of any GP consultations they may have had in the 12 months before diagnosis. In addition, a cohort of children without T1D but matched for age, gender, location, socioeconomic class, GP and another acute illness (e.g. infection) will be identified to explore the specificity and predictive potential of variables related to development of T1D.

The first stage of the study will involve identifying all children (i.e. those under 15yrs of age) diagnosed with T1D from 1st January 2000 to 31st December 2015 in the Brecon Group Register and categorising them into those who presented with or without DKA at diagnosis. Extrapolations from the Welsh data suggest that there will be approximately 3500 children diagnosed with T1D in these years, with at least 700 children who presented in DKA. The SAIL research analyst will link these data with the GP dataset from the SAIL databank using:-

- First and last name
- Gender
- Date of birth
- Date of diagnosis
- DKA status
- GP practice
- Postcode (NHS number is not recorded in the Brecon Group Register).

The dataset generated from this process will be anonymised using an ALF, ensuring the researchers do not have access to any personal identifiable data (e.g. age at diagnosis in DKA will be calculated using date of birth and date of diagnosis and then date of birth will be discarded). In addition, a cohort of controls presenting to their GP with acute illness but who do not have T1D will be identified from SAIL at the ratio of 3:1. This cohort will be matched to the T1D cohort by:-

- Age
- Gender
- GP practice

The SAIL analyst will extract the following information:-

- All GP consultation records in the 12 months prior to diagnosis for children diagnosed with T1D
- All GP consultation records of the matched cohort of children without T1D. (This cohort will be matched on the date they presented to their GP with an acute illness. This will act as the time point for consultations in the previous 12 months.)

Within the consultation records variables will include:-

- Symptom details
- Diagnoses
- Tests undertaken
- Medication prescribed
- Co-morbidities

Demographic factors collected

- Children
  - Age at diagnosis
  - Gender
  - Deprivation quintile (based on postcode)
  - GP practices
  - List size
  - Number of GPs within the practice.

Initial analysis of the dataset will assess and explore the read codes attached to each GP consultation in the 12 months before diagnosis. The researchers will define the read codes and explore mechanisms for grouping symptoms to allow for meaningful clinical interpretation. Each patient's prodrome (the 12 months before diagnosis) will be assessed by analysing the number of GP visits, symptoms, diagnoses, tests undertaken and treatments given.

15 Statistical considerations

- **Randomisation**

Not applicable

- **Sample size**

As the primary purpose of this study is to seek an earlier diagnosis of T1D, the study is powered for the case-control study. Assuming a medium effect size (OR=1.5), a moderately low prevalence rate of the risk factor 30% in the control group, matching 3 controls per case and using a two sided 5% alpha and 80% power, we will require 322 children with T1D. If a total of around 390 children diagnosed with T1D were identified between 2010 and 2012 this would give the study over 90% power. A secondary aim of the study is to explore the risks associated with presenting in DKA (or not). Given that approximately 23% of children diagnosed with T1D are in DKA at diagnosis then we have 90 children in DKA and 300 not in DKA, we will not be powered to observe any small to medium effect sizes for any risk factors. This analysis will be exploratory in nature.

16 Analysis

- **Main analysis**

The two groups will be described using summary statistics (N (%), mean (sd), median (inter-quartile range)) for the explanatory variables identified as described above. Predictors of presenting in DKA at diagnosis (using the explanatory variables identified) will be examined using a two-level logistic regression model (children within practice). Where numbers allow, variation in DKA will be accounted and corrected for at the level of general practice. Associations between the prodromes for children presenting in DKA will be examined firstly at the univariable level and significant predictors (with a P-value <0.10) retained for the multivariable model. Odds ratios (ORs) will be estimated together with 95% confidence intervals (CIs).

The quality of the matching will be examined by describing the case-mix (with respect to age, gender, co-morbidites and practice factors) of the case (T1D) and control (general population of children) groups. The two groups will be also be described to examine any differences in prevalence of presentation of such symptoms, GP visits, tests and medications in primary care. A similar analysis will be used as in the T1D analysis only using a conditional logistic regression model to account for the non-independent observation created by matching, and results again presented as ORs alongside 95% CIs.

- **Data storage & retention**

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network.

17 Study closure

The end of the study will be considered as the date of the submission of the final report.

18 Regulatory issues

- **Ethical and research governance approval**

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The study will be submitted to an NHS Research Ethics Committee (NHS REC) for approval. This is consistent with the requirements of Cardiff University who will be requested to act as the study sponsor.

- **Consent**

Informed consent will not be sought from participants, as the data being used is anonymised and patients who contribute to the Brecon Group register provide consent for their data to be used for research purposes.

- **Confidentiality**

The Chief Investigator and the research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998.

- **Indemnity**

Cardiff University will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. Cardiff University does not provide compensation for non-negligent harm.

- **Study sponsorship**

Cardiff University will act as sponsor for the study.

- **Funding**

This study has been funded by the Novo Nordisk UK Research Foundation.

- **Audits & inspections**

The study may be participant to inspection and audit by Cardiff University under their remit as sponsor.

19 Study management

Project team meetings and Study Management meetings

The project team meetings and SMG will consist of the Chief Investigator and the co-applicants. The role of the SMG will be to assist in the study set up by providing specialist advice, input to and comment on the study procedures and documents (protocol etc). They will also advise on the promotion and the running of the study and deal with any issues that arise. The group will meet, either face-to-face or using audio-conferencing facilities, as required throughout the course of the study. All SMG members will be required to sign up to the SEWTU SMG charter.

20 Data monitoring & quality assurance

Not applicable

- **SSC (Study Steering Committee)**

A SSC will not be established for this study.

- **DMC (Data Monitoring Committee)**

A DMC will not be established for this study.

21 Publication policy

The publication policy will be drafted and approved by the Study Management Group. It will state principles for publication, describe a process for developing output, contain a map of intended outputs and specify a timeline for delivery. The publication policy will respect the rights of all contributors to be adequately represented in outputs (e.g. authorship and acknowledgments) and the study to be appropriately acknowledged.

22 Milestones

Study timelines will be detailed in the Study Gantt chart.

23 References

1. Patterson CC, Dahlquist GG, Gyurus E et al. (2009) Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005 – 20: a multicentre prospective registration study. Lancet. 373:2027-33
2. Gardner SG, Bingley PJ, Sawtell PA et al (1997) Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's Oxford Study Group. BMJ. 315: 713-17
3. Ali K, Hamden A, Edge JA. (2011) Type 1 diabetes in children. BMJ; 342:d294
4. Usher-Smith JA, Thompson MJ, Walter FM (2013) Looking for the needle in the haystack: a qualitative study of the pathway to diagnosis of type 1 diabetes in children. BMJ Open.
5. Edge JA, Ford-Adams ME, Dunger DB (1999) Causes of death in children with insulin dependent diabetes 1990 – 96. Arch Dis Child; 81:318-23

6. Wales online http://www.walesonline.co.uk/news/wales-news/charity-appeal-launched-memory-cardiff-8431898
7. Icks A, Strassburger K, Baechle C, Rosenbauer J, Giani G, Beyer P, Holl RW. (2013) Frequency and cost of diabetic ketoacidosis in Germany – study in 12,001 paediatric patients. Exp Clin Endocrinol Diabetes. 121(1):58-9
8. Shrestha SS, Zhang P, Barker L, Imperatore G. (2010) Medical expenditures associated with diabetes acute complications in privately insured U.S. youth. Diabetes Care. 33(12):2617-22
9. Bowden SA, Duck MM, Hoffman RP. (2008) Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. Pediatr Diabetes. 9(3 Pt 1): 197-201
10. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. (2015) Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes. 64(2):631-42
11. National Paediatric Diabetes Audit Project Board, Royal College of Paediatrics and Child Health (2014) National Paediatric Diabetes Audit Report 2011-12 Part 2 Hospital admissions and complications
12. King BR, Howard NJ, Verge CF, et al (2012) A diabetes awareness campaign prevents diabetic ketoacidosis in children at their initial presentation with type 1 diabetes. Pediatr Diabetes. 13(8): 647- 51
13. Vanelli M, Chiari G, Ghizzoni L, et al (1999) Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes Care. 22:7-9
14. Lansdown AJ, Barton J, Warner J et al (2012) Prevalence of ketoacidosis at diagnosis of childhood onset Type 1 diabetes in Wales from 1991 to 2009 and effect of a publicity campaign. Diabet Med. 29 (12): 1506-9
15. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM (2011) Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ. 7: 343
16. Sayers A, Thayer D, Harvey J et al (2015) Evidence for a persitant, major excess in all cause admissions to hospital in children with type 1 diabetes: results from a large Welsh national matched cohort study. BMJ Open. 13;5(4)