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WILEY ISPAD International Society for Pediatric and Adolescent Diabetes

ORAL SESSIONS

Oral Session I - Psychosocial Issues

O01
Crowdsourced design of an online coping intervention for parents of very young children with type 1 diabetes

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Objectives: Parenting very young children with Type 1 diabetes (T1D) is immensely challenging. We collected and analyzed extensive crowdsourced qualitative data from a "Parent Crowd" of 166 parents of children diagnosed with T1D before the age of 6 years. Those perspectives are now guiding the design of an online coping intervention for this population. This presentation updates progress made in translating parent perspectives into a website that will be tested in a rigorous clinical trial.
Methods: With ongoing input from the Parent Crowd, the research team (including six Family Advisors) and web developers met regularly beginning in Winter 2015 to translate parent perspectives into a functioning website. Website goals were

1. Ensure parents/caregivers have the information, resources, and support needed to promote the health and well-being of their young children with T1D and
2. Provide parents/caregivers of young children with T1D the information, support and resources they can use to enhance their own l health and well-being.

Results: Principles of User-Centered Design and extensive Parent Crowd input guided all phases of the development of the online resource. We generated a conceptual framework that defined the content areas to be addressed, a list of operating principles, and functional specifications for the resource. Collaboration with web development strategists yielded a taxonomy of search terms by which users will search and navigate the website; a sitemap; a content management strategy; and wireframes to guide the architecture, construction and functionality of the internet resource.
Discussion: This presentation illustrates principles of user-centered design in the process of creating an online coping intervention for parents of children under age 6 with T1D. Once the design and development of the website is complete, the researchers will conduct a randomized controlled trial of intervention effects on a range of child and parent outcomes.

O02
Characterizing diabetes burnout in parents of youth with type 1 diabetes (T1D)

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Objective: Managing T1D is complex and requires round-the-clock attention, much of which falls to parents. Parental stress and family conflict about diabetes are associated with suboptimal youth self-management and glycemic outcomes, yet little research has described parents' experiences with burnout or tested distress-reduction interventions for parents. A nuanced understanding of parents' feelings about T1D burnout may inform interventions to offer support, enhance parental quality of life, and potentially impact youth outcomes. This study aimed to characterize diabetes burnout in parents of youth with T1D.
Methods: As part of a larger qualitative study on diabetes-related quality of life, 21 parents (90% female; 38% Caucasian) of youth (age 4-17) with T1D answered semi-structured interview questions, including questions about their feelings around T1D management demands. Interviews were audio-recorded, transcribed, and coded to derive central themes.
Results: Parents described:

1. worries about their children experiencing burnout due to the substantial daily demands of T1D management;
2. burnout related to their own physical and emotional exhaustion from juggling T1D care with other domains of life; and
3. a negative impact of their burnout on family relationships, including frequent arguments and lack of time to strengthen these relationships.

Conclusions: Parents of youth with T1D often struggle with diabetes burnout, which may affect many domains of their lives and impact their children and family relationships. Screening for and acknowledging parental burnout as part of routine T1D care may help support effective family T1D management. For some parents, referrals to mental health providers familiar with parenting a child with a demanding chronic illness may be useful to manage diabetes burnout and improve quality of life, which may ultimately impact youths' diabetes outcomes.

O03
Establishing clinical cutoffs for the hypoglycemia fear survey

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Objective: Determine clinical cutoffs for the Hypoglycemia Fear Survey (HFS) in mothers of young children and adolescents with type 1 diabetes (T1D).
Methods: Mothers (N = 1,145) completed either the HFS-Parent (HFS-P; child age >8 years) or HFS for Parents of Young Children (HFS-PYC; child age < 8 years). Clinical cutoffs were determined

using the mean±1 SD for Maintaining High Blood Glucoses, Worry/Helplessness About Low Blood Glucoses, and Worry About Social Consequences subscales. CSII blood glucose (BG) data were downloaded for a subset of children.
Results: Clinically elevated and absence of fear of hypoglycemia (FOH) cutoffs are in the Table. For mothers of young children, less worry/helplessness was associated with greater percentage of high BGs ($r = 0.24$, $p < 0.01$). Being a parent of a girl was related to more worry/helplessness ($r = 0.28$, $p < 0.01$). Being the mother of an adolescent boy was associated with more worry about social consequences ($r = 0.28$, $p < 0.01$), but not BG.
Conclusions: Here, we propose clinical cutoffs for the HFS that are empirically determined and show preliminary concurrent validity with children's BG. With these cutoffs, it is now possible to identify mothers with clinically elevated FH and those who have extremely low FOH, both potential risk factors for optimal glycemic control. These cutoffs now allow for the HFS to be used as part of T1D annual screening for anxiety as recommended by the American Diabetes Association and to make referrals for treatment.

	HFS-P		HSF-PYC	
	+1 SD	- 1 SD	+1 SD	- 1 SD
Maintaining High Blood Glucoses	7	2	8	2
Worry/Helplessness About Low Blood Glucoses	24	9	19	11
Worry About Social Consequences	9	1	13	3

Clinical Cutoffs for the Hypoglycemia Fear Scale

O04
Reducing hypoglycemia fear in parents of young kids with type 1 diabetes (T1D) using video-based telemedicine: preliminary findings from REDCHiP

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Objectives: Fear of hypoglycemia (FH), common among parents of young children with T1D, can prevent achievement of glycemic control targets. We present preliminary findings from a pilot randomized control trial that uses a video-based telecommunication platform to reduce hypoglycemia fear in parents of 1-6 year-olds with T1D.
Measures: Parents completed ten 1-hour sessions (7 group, 3 individual) which used a cognitive-behavioral approach to reduce hypoglycemia fear and increase adaptive parenting for T1D. Twenty-six parents have been randomized to treatment or waitlist control so far, and 19 have completed the trial. Here, we report on data from 17 parents (Parent age = 35.2±5.3 yrs; 95% Mothers; Child age = 4.6±1.3 yrs; 90% White; time with T1D 24.1+13.9 mo). Pre- and post-treatment, parents completed the Hypoglycemia Fear Survey-Parents of Young Children, Pediatric Inventory for Parents, Center for Epidemiological Studies Depression Scale, and Parental Self-Efficacy Scale for Diabetes Management. Child HbA1c (fingerstick) was also measured via HPLC using a central lab.
Results: Parents completed 93% of treatment sessions and reported significant pre-post reductions in hypoglycemia worries ($t = 3.66$, $p = .003$), maladaptive behaviors to prevent a low ($t = 3.99$, $p = .001$), as well as the frequency ($t = 2.25$, $p = .04$) and intensity ($t = 3.50$, $p = .003$) of parenting stress related to their child's T1D. There were no significant changes in parental self-efficacy or depression. Mean HbA1c pre- and post-treatment was 8.32±1.15 (67 mmol/mol) and 8.05±0.83 (64 mmol/mol), respectively, indicating a modest, but non-significant decrease.
Conclusions: Our findings show preliminary efficacy for the REDCHiP intervention to reduce parents' hypoglycemia fear, maladaptive parenting behaviors, and T1D-related stress, which all may impair T1D management. The high visit completion rate suggests that video telehealth can reduce geographic and logistic barriers when offering T1D interventions to families.

O05
Maternal behaviors to monitor for type 1 diabetes in children genetically at risk in the TEDDY study: impact of first positive islet autoantibody test result

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Objective: To examine change in maternal behaviors to monitor for clinical onset of type 1 diabetes (T1D) in children at genetic risk for T1D when told of first positive islet autoantibody (IA+) result.
Methods: The Environmental Determinants of Diabetes in the Young (TEDDY) Study follows 8676 children with high-risk HLA-DQ genotypes from birth to age 15. IA was tested quarterly up to age 4 years and biannually thereafter. First IA+ before the child was 7 years of age occurred in 839 families. Monitoring was assessed before/after seroconversion with the item "Have you done anything to monitor or keep an eye on your child's risk of developing diabetes?" Responses were coded. Factors independently associated with change in behavior were examined using multiple logistic regression, adjusting for country, T1D family history, and minority status.
Results: Of 839 families with IA+ result, 373 mothers were not monitoring before seroconversion. Of these, 152 (40.8%) began monitoring after first IA+ result (Figure 1). Having a younger child ($p = 0.02$), accurate T1D risk perception ($p = 0.049$), and higher anxiety ($p < 0.001$) were associated with initiating monitoring behaviors.
Conclusion: Many mothers view TEDDY tasks as a way to monitor for T1D, a positive consequence of participation in an observational study with no intervention offered. After IA+ notification, some mothers initiate monitoring behaviors; particularly, watching for T1D symptoms and blood glucose checking increases.

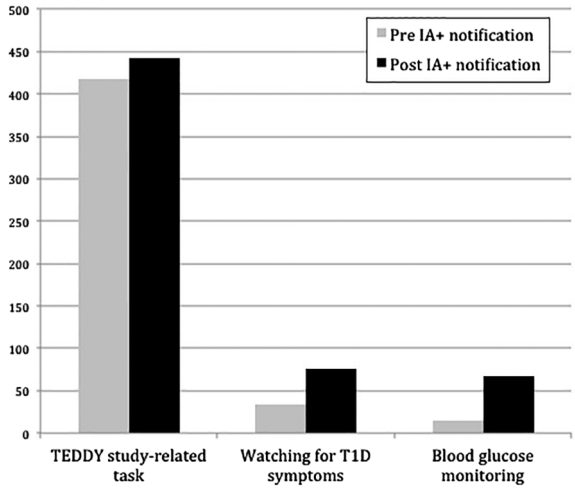

Figure 1. Monitoring behaviors reMonitoring behaviors reported by mothers pre/post IA+ notification.

O06

Perspectives of adolescents with type 1 diabetes (T1D) on diabetes well-being

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Objectives: Diabetes clinical trials increasingly use patient-reported outcomes (PRO's) in addition to glycemic/health outcomes. However, there currently is no measure of adolescent diabetes well-being that has been based on the perspectives of teens with T1D.
Methods: An international panel of pediatric endocrinologists; psychologists, educators, RNs and RDs used their collective clinical experiences to construct a well-being survey for teens with T1D. The initial 24 survey items measure self-worth; diabetes distress/worry; communication; social/peer integration; weight/body image; and family, with a 5-point Likert response scale. To assess the relevance and acceptability of this provider-designed survey in teens with T1D, 36 teens (18 younger [13-15 yrs] and 18 older [16-18 yrs]) with T1D, with wide-ranging A1c values (<7->10%) in 2 US diabetes centers completed the survey and then responded to a standardized cognitive interview by trained research staff. Interviews were audio-recorded and analyzed for common themes about item clarity, acceptability and importance.
Results: Teens (50% male) had mean age 16 yrs, T1D duration 10 yrs; most were pump-treated. Analyses of cognitive interviews revealed that there was strong consensus that survey items about weight/body image and peer relationships were not relevant to their diabetes well-being, whereas items about family interactions, motivation and support for T1D self-care were most important. In response to this strong preference for items about family, motivation, and support, the well-being survey was revised and shortened to 12 items.
Conclusions: While peer and body image issues are part of normal teen development, teens with T1D gave more importance and relevance for their diabetes well-being to items addressing family interactions and motivation for self-care. Findings emphasize the importance of involving pediatric "patients" in the design of "PRO's".

O07

Interactions among adolescent and young adult patients with type 1 diabetes and their health care providers: implications for glycemic control

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Objective: Adolescents and young adults (AYAs) with type 1 diabetes (T1D) must assume increasing independence for health care tasks, including taking initiative and leading interactions with health care providers (HCPs). This study utilizes objective and subjective ratings of health care interactions to examine associations among the quality of AYA-HCP interactions, adherence, and glycemic control.
Methods: Seventy-five AYAs (M age = 17.81; 55% female; 51% Caucasian) with T1D enrolled in an observational study evaluating AYA-HCP communication. Diabetes outpatient clinic visits were audio-recorded and coded using the Roter Interaction Analysis System (RIAS). AYA participants completed self-report measures, including the Health Care Climate scale (HCC) and the Self-Care Inventory (SCI). A1c was extracted from the medical record; mean A1c was 8.86% (±2.23).
Results: Clinic visits averaged 21.50 min (±10.21). HCP talk exceeded AYA talk (384.10 utterances vs. 129.29 utterances). Ratings of interaction quality were associated with glycemic control. Controlling for visit length and age, higher AYA interactivity and AYA interest/attentiveness correlated with lower A1c; further, lower HCP dominance and higher HCP warmth correlated with lower A1c (all ps < .05). Path analysis supported the importance of high-quality interactions. Higher AYA-rated health care climate (e.g. encouraging questions) was significantly associated with better T1D adherence which, in turn, was related to lower A1c (overall model p < .05).
Conclusions: High quality AYA-HCP interactions are associated with better T1D health indicators. Specialists working with AYA patients can encourage AYA engagement with HCPs, including support for asking questions and joining in shared decision making. Future research should examine these associations over time, particularly the stability of the quality of AYA-HCP interactions and using the quality of the AYA-HCP relationship to predict later glycemic control.

O08

Participation in every day life of children and adolescents with type 1 diabetes - restrictions identified using the WHO's International Classification of Functioning, Disability and Health (ICF)

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Objective: To assess participation in every day life in young patients with type 1 diabetes (T1D) compared to healthy peers and to identify risk factors influencing participation
Methods: Two questionnaires (SPS-24/7 and ICF-D) based upon WHO's International Classification of Functioning, Disability and Health (ICF) were used to assess participation. Medical data was obtained from clinical records documented in the DPV (Diabetes Patienten Verlaufsdokumentation). 105 T1D patients (53.3% male, mean 12.83±2.04 years) were compared to 649 healthy controls (44.3% male, mean 11.92±2.80years). The influence of metabolic control (HbA1c≤7.5% vs. HbA1c>7.5%), therapy regimes (CSII vs MDI) and diabetes complications (severe hypoglycemia and/or DKA) was assessed.
Results: There were differences between T1D patients and healthy controls in "Higher Level Cognitive Functions" (p = .037).

Patients with CSII showed restrictions in "Sports" (p = .028), "Impulse Control" (p = .016) and "Interpersonal Interactions" (p = .006). Patients with HbA1c>7.5% had lower scores in "Self-Care" (p = .012), "Higher Level Cognitive Functions" (p = .031), "Writing" (p = .024) and had to repeat classes in school three to eight times more often (p = .007) than patients with HbA1c≤7.5% or controls.

The highest rates of restrictions were observed in the group of patients with T1D complications in "Interpersonal interactions and relationships" (p = .024), "Communication" (p = .038), "Attention Functions" (p = .020), "Self Care" (p = .045), "Temperament and Personality Functions" (p = .010), "Energy and Drive Functions" (p = .048), "Recreation and Leisure Functions" (p = .030) and in "Mobility" (p = .035). Furthermore patients with complications repeated classes four times more often than patients without complications (p = .036) or healthy controls (p = .006)
Conclusions: While T1D patients in general show good participation scores, patients with T1D complications were identified to be at risk of having serious restrictions in every day life.

Oral Session II - Diabetes Education

O09

Home telemedicine significantly improves adherence to medical appointments in young adults with type 1 diabetes

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Objectives: To determine if the completion of home telemedicine appointments (CoYoT1 Clinic) in young adults with type 1 diabetes (T1D) improves the frequency of follow-up, retention in care, and adherence to American Diabetes Association (ADA) guidelines regarding appointment frequency.
Methods: CoYoT1 Clinic was designed to meet the diabetes care needs of young adults with T1D through home telemedicine. Visits occurred every 3 months over the one-year study, with patients being seen 3 times by home telemedicine and 1 time for an in-person visit. Outcomes were compared to patients receiving treatment as usual (control).
Results: Mean age of CoYoT1 patients was 19.9 years and 20.4 years in controls. Both groups were 53% female with the majority of patients being non-Hispanic (89%, 81%) and White (87%, 91%) in CoYoT1 patients and controls, respectively. Compared to controls, CoYoT1 patients attended significantly more clinic visits, $t(86) = 11.03$, $p < 0.0001$, and increased their visit number from the year prior to the intervention. Seventy-one percent of CoYoT1 patients were seen 4 times over the study year, meeting ADA guidelines, but no patients in the control group met the ADA recommendation.
Conclusions: Delivering diabetes care by home telemedicine increases young adult adherence to ADA guidelines and improves retention in care when compared to controls. Home telemedicine may keep young adults engaged in their diabetes care during this challenging transition period.

Variable	CoYoT1 Intervention (n = 45)	Control Patients (n = 43)	p-value
Mean Number of Clinic Visits in Year Prior to Study (SD)	2.4 (1.3)	2.1 (1.2)	0.33
Mean Number of Clinic Visits in 1-year Study (SD)	3.4 (1.1)	1.0 (0.9)	<0.0001*
Patients seen at least 4x per year - N (%)	32 (71%)	0 (0%)	<0.0001*
Clinic Attendance			
Clinic 1	44 (98%)	4 (9.3%)	<0.0001*
Clinic 2	39 (87%)	4 (9.3%)	<0.0001*
Clinic 3	35 (78%)	9 (21%)	<0.0001*
Clinic 4	35 (78%)	8 (19%)	<0.0001*
Clinic 5	—	19 (44%)	—

[Clinic Attendance]

O10

Interest and acceptability of DiVE (Diabetes Virtual Education), a serious game dedicated to diabetes education in type one diabetes (T1D)

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Objectives: The use of video games appears suitable and interesting to respond to the increase need for diabetes education in children and adolescent with T1D. DiVE is a serious game that brings knowledge to paediatric patients thanks to video, games and simulation in a numeric environment. Patients can also express their experience thanks to a social network.
Methods: Pilot study (11 weeks - 3 months - 11 paediatric centres) to evaluate interest, playability and acceptability of DiVE as a support for diabetes education. Data recorded: number of connections, total time of connection, percentage of success in included assessment. Satisfaction survey at the end of the study.
Results: 33 patients have logged on to the game at least 3 times. B/G: 51/49% - Median Age 12.5 years (9.5 to 18). 425 recorded connexions (309 in the first month, 83 in the second, 33 in the third) an average of 6 connexions per day. Progress through the game ranged from 2 to 76%, most of the patients completed at least 20% of the levels. Total connexion time was 5 days 2 hours and 43 minutes. Percentage of success in assessment quizz ranged from 49 to 67%. 75% of the patients liked the game graphics and 66% found it easy to use. 80% found the content interesting and it brought a better understanding of the disease to 70% of the participants. 53% said that the game has helped them to better understand their blood glucose changes and 81% reported the social network to be helpful.
Conclusion: DiVE can be used as a support for diabetes education in children and adolescents to provide knowledge and to promote self-administered care. This study also showed that the number of level must be reduced and the content of some educative videos further simplified. The in game training program should be less linear to allow a direct access to all content. A moderation of the virtual community created by the game is also critical to sustain patients´ interest and to allow them to share their experience.

O11

Democratizing diabetes knowledge In rural and underserved communities: endocrinology TeleECHO Clinic (Endo ECHO)

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Objective: (1) Democratize specialty knowledge and expand diabetes patients´ access to specialty services in the setting of limited access to medical recourses, (2) Demonstrate proof of concept for adaptation of Project ECHO (Extension for Community Healthcare Outcomes) model to include patients with diabetes.
Methods: The Endocrinology TeleECHO Clinic (Endo ECHO) model develops knowledge and capacity among community health workers through:

1. Using technology to leverage scarce resources and create knowledge networks, which connect a multidisciplinary team of experts located at the "Hub" with learners, who have direct patient access, at "Spoke" through regularly scheduled teleECHO clinics;
2. Improving outcomes by reducing variations in processes of care and sharing best practices;
3. Case-based learning: guided practice through diverse, real-life cases with subject matter experts to facilitate learning by doing and create learning loops;
4. Tracking of data to measure clinic function over time for the purposes of ongoing quality improvement.

Results: This 3-year, prospective case-control cohort design will evaluate health outcomes as well as cost-effectiveness associated with the Endo ECHO intervention. Baseline demographic characteristics of 373 participants enrolled to date in New Mexico: majority patients (92%) have type 2 diabetes and approximately half are Medicaid (low income) beneficiaries.
Conclusions: Endo ECHO is an implementation of an innovative healthcare delivery model which builds capacity for treatment of complex diabetic patients in medically underserved communities. The current study design will demonstrate whether, and to what extent, Endo ECHO improves health outcomes for complex diabetic patients living in rural New Mexico, and will serve as proof-of-concept for academic medical centers wishing to replicate the model. The ECHO model could serve as a disruptive delivery model for pediatric diabetes in developing countries.

O12
Examining subgroup differences of treatment effects in the resilient, empowered, active living with diabetes (REAL Diabetes) study

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Objectives: The REAL Diabetes Study was an RCT that demonstrated the efficacy of an occupational therapy intervention in improving A1C and diabetes quality of life (DQoL) among low-SES young adults in the United States. We evaluated differences of intervention effects between sub-populations based on baseline variables.
Methods: 81 participants age 18-30 with type 1 or type 2 diabetes (T1D/T2D) were randomized to the REAL intervention (IG) or an attention control group (CG). Separate regression models were created to analyze effect modification of treatment effects on A1c and DQoL for each of the potential effect modifiers: diabetes type, ethnicity, gender, and recruitment setting.
Results: There was no significant effect modification for changes in A1c or DQoL (Table 1). Still, there was a marked difference in the A1c trajectories based on diabetes type: for participants with T1D, the IG had a decrease in A1c (-0.84%) and the CG had no change in A1c (-0.03%). However, for participants with T2D, the IG showed a modest increase in A1c (0.2%) and the CG had a large increase in A1c (1.58%).
Conclusion: While the REAL intervention did not demonstrate significant differences in efficacy amongst population subgroups, our findings echo recent literature showing that youth-onset T2D is more aggressive and challenging to manage than T1D. More research is needed to identify effective clinical and behavioral interventions to support this population in maintaining glycemic control.

O13
Carbohydrate (CHO) counting and type 1 diabetes (T1D): RCT of internet-based teaching for those learning to count

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Principles of CHO counting are traditionally taught during face-to-face sessions with a dietitian. While web-based learning programs in diabetes education may capitalize on teenagers' comfort with technology and help advance skills in diabetes management, these programs have not been studied in teens.
Objective: To compare CHO counting accuracy in adolescents with T1D after face-to-face education or an internet-based video tutorial.
Method: Adolescents aged 12-17 years with T1DM (for >1 year) who self-identified as non-CHO counters were recruited from the SickKids Diabetes Clinic. Adolescents completed the Peds Carb Quiz (PCQ) and evaluated the CHO content of test trays (3 meals + 3 snacks) that were randomly assigned. Paired t-tests were used for comparing pre and post data. Univariate and multivariate regression was conducted to determine factors related to accuracy of counting and PCQ score.
Results: 50 participants (23 female), age 14.8 ±2.1 yrs, HbA1c 9.1% ±1.8%, T1DM duration < 8 yrs - 62% and >8 yrs -38%, insulin

	Intervention Group: Baseline (A1C/QOL)	Intervention Group: Follow-Up (A1C/QOL)	Intervention Group: Change (A1C/QOL)	Control Group: Baseline (A1C/QOL)	Control Group: Follow-Up (A1C/QOL)	Control Group: Change (A1C/QOL)	p-value (A1C/QOL)	p-value for interaction (A1C/QOL)
Overall	11.01/-2.44	10.47/-1.84	-0.57/0.70	10.51/-2.78	10.80/-2.53	0.36/0.15	0.01/0.04	n/a
T1D	10.69/-2.52	9.84/-1.99	-0.84/0.78	10.44/-2.83	10.35/-2.54	-0.03/0.23	0.05/0.10	0.54/0.63
T2D	12.02/-2.18	12.22/-1.35	0.20/0.44	10.71/-2.61	12.21/-2.49	1.58/-0.07	0.10/0.18	0.54/0.63
Latino	11.09/-2.41	10.65/-1.75	-0.46/0.70	10.41/-2.41	11.00/-2.44	0.65/-0.12	0.002/0.01	0.19/0.18
Non-Latino	10.60/-2.61	9.26/-2.34	-1.28/0.72	10.74/-3.64	10.33/-2.72	-0.34/0.80	0.87/0.91	0.19/0.18
Female	11.04/-2.70	10.57/-2.31	-0.52/0.75	10.51/-2.83	10.75/-2.53	0.33/0.16	0.05/0.19	0.93/0.71
Male	10.99/-2.14	10.37/-1.47	-0.62/0.67	10.38/-2.77	10.73/-2.70	0.35/0.07	0.22/0.09	0.93/0.71
In-Clinic	11.02/-2.11	10.47/-1.57	-0.51/0.65	10.19/-2.47	10.41/-2.22	0.26/0.24	0.11/0.17	0.78/0.79
Social Media/Mailings	11.01/-2.75	10.46/-2.11	-0.63/0.76	10.86/-3.12	11.26/-2.89	0.48/0.05	0.06/0.10	0.78/0.79

[Treatment Effects by Subgroup: A1C and QOL]

regimen: Pump 18.4%, MDI 26.5%, TID 51%, BID 4.1%. Baseline PCQ scores for the entire group was 73%± 0.15%and absolute difference between actual CHO content and estimated content was 20.6±12.5 g (meals), and 5.8±6.4 g (snacks). Overall, the two groups did not differ in terms of change in PCQ score (β = 3.13, 95% CI -0.36, 6.61, p = 0.076) or in CHO counting accuracy (β = -5.04, 95% CI-13.83, 3.76, p = 0.25). On multivariate analysis of CHO counting accuracy, HbA1c was the only significant factor associated with accuracy (Odds ratio = 0.68, CI 0.51-0.91). For every A1C increase of 1%, patients became 32% less likely to count accurately (p = 0.0081).
Conclusion: Overall, children with T1D who did not regularly CHO count performed well on CHO count assessments. There were no significant differences between teaching modalities, nor overall change in CHO knowledge. Most recent HbA1c was the sole predictor of CHO counting accuracy.

O14
Educating teachers about diabetes - a retrospective analysis of a program making its mark

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Introduction: Diabetes Victoria (DV) has a long history of actively working to increase the confidence of teachers in Victoria to support children (3-18 yrs) with type 1 diabetes (T1D) to learn and achieve their academic potential. In 2017 there are 2740[a] Victorian children in this age group.

In 2007 DV commissioned an independent report with recommendations made including the need to "Develop a type 1 diabetes training and support program for all Victorian schools". As a result the Diabetes at School and Preschool Program (DSPP) was developed in collaboration with the two largest paediatric hospitals in Melbourne, and launched in 2009. The program was endorsed by the State's Department of Education and Training and is embedded within their policy framework.
Objective: To examine retrospectively the reach and effectiveness of the DSPP to increase teacher knowledge and confidence to support students with T1D.
Method: A mixed method design was conducted involving a retrospective analysis of the DSPP's model across Victorian primary, secondary and preschool settings; and a cross sectional survey of recent participants.
Results: From 2009 to April 2017 DV has run 91 programs for 2796 staff from school and early childhood settings. Increased demand has led to a greater number of programs being run each year. To improve reach, a train-the-trainer model was implemented in 2012; in 2017 there are now nine external regional centres delivering the program across Victoria.

Post-program surveys collected in 2017 from 383 participants identified that 97% were highly satisfied with the program with 98.4% having increased knowledge of diabetes. Confidence scores for essential T1D care aspects showed 99.7% report an increased awareness of hypoglycaemia symptoms, and 100% know what to do if a child has a hypo at school.
Conclusion: The demand and effectiveness of the DSPP is clear, and the challenge is now to continue to expand the reach of this program nationally.

[a]NDSS, May 2017

O15
Colorado competency framework for diabetes care in schools: preparing a skilled school health workforce

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Objective: To develop a competency framework for diabetes care in schools.
Method: A modified Delphi, consisting of 3 rounds of online surveys, was completed with 37 school nurses, health aides, school health leaders and health care providers. The purpose was to seek input and group consensus about what competencies (knowledge and skills) should be assumed by varying levels of health staff: health aid, district nurse and regional nurse. The initial survey included competencies established by the American Association of Diabetes Educators, modified for relevance to the school setting. Participants provided feedback and rated competencies for necessity and appropriateness. Consensus was defined as >80% agreement that a competency was important for diabetes care at school.
Results: Response rates were high (>90%) for all 3 rounds. Consensus about the importance of 71 competencies in the school setting was obtained across 6 categories: Diabetes Care Tasks (14), Teaching and Diabetes Management Support (14), Clinical Practice (14), Pathophysiology (13), Epidemiology (6), and Professional Development (10). Examples of selected competencies are shown in the figure.
Conclusion: The modified Delphi is an effective method for determining appropriate competencies for a school setting. The resultant framework can be used to develop diabetes education programs. Based on the identified competencies, a diabetes education program for school nurses and health aides is in development.

Colorado Competency Framework for Diabetes Care in Schools: Selected Competencies

DIABETES CARE TASKS	Health Aide	District Nurse	Regional Nurse
Demonstrates correct insulin preparation, administration, and storage	X	X	X
Follows protocol for treatment of mild, moderate, and severe hypoglycemia	X	X	X
Describes insulin action		X	X
TEACHING AND DIABETES SELF-MANAGEMENT SUPPORT	Health Aide	District Nurse	Regional Nurse
Identifies and refers questions and/or need's of the student/family to the appropriate school health team member	X	X	X
Teaches, reinforces, and validates diabetes self-management skills		X	X
Develops an individualized diabetes management support plan in collaboration with family/student		X	X
Serves as a resource in curriculum development and maintenance, program planning, implementation and evaluation			X

Continued

CLINICAL PRACTICE	Health Aide	District Nurse	Regional Nurse
Follows work-place specific clinical practice protocols applicable to diabetes management	X	X	X
Develops or revises diabetes education and support policies and procedures according to the standards of diabetes care		X	X
Collaborates with stakeholders to ensure schools have the resources to provide diabetes training and delegation			X
PATHOPHYSIOLOGY	Health Aide	DistrictNurse	Regional Nurse
Explains the signs and symptoms of acute hyperglycemia and diabetic ketoacidosis (DKA)	X	X	X
Describes the differences between type 1 and type 2 diabetes	X	X	X
Applies knowledge of diabetes pathophysiology to direct diabetes education, school staff training and/or diabetes care		X	X

[Colorado Competency Framework for Diabetes Care in Schools: Selected Competencies]

O16
The Impact of the diabetes education to teachers on diabetes management of children with type 1 diabetes in the school setting

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Objectives: The presence of educated staff in the school plays a critical role in the prevention of acute and chronic complications of diabetes. The aim of this experimental designed study is to determine the impact of the diabetes education to teachers on diabetes management of children with type 1 diabetes in the school setting.
Methods: Participants were 44 primary school students with Type 1 Diabetes (20 in intervention group, 24 in control group) and their teachers, randomly selected from the Children's Diabetes outpatient clinics of two hospitals in Istanbul, Turkey. The "Diabetes Management at School" course was provided to the teachers of the students in the intervention group. The content of the "Diabetes management at school" education program for teachers was established in line with the pre-test results obtained from the participants. Before and a month after the training, teachers diabetes knowledge was measured. Before and 3 months after the training intervention and control groups were questioned about hyperglycemia and hypoglycemia at school and home, and HbA1c values were also assessed.
Results: One month after the training, teachers' diabetes knowledge scores were high ($p < 0,01$). The level of teachers' ability to cope with their students' diabetes were found significantly higher after the training ($p < 0,001$). The incidence of hyperglycemia at the school in the intervention group after diabetes training to teachers was decreased ($p < 0,001$). After the training given to teachers, -0,36 reduction was observed in HbA1c levels in the intervention group, while there was an increase of 0.59 in the control group, and it was determined that this difference was statistically significant ($p < 0,01$).
Conclusions: Diabetes education to the diabetic student's teachers make a positive contribution to students' metabolic control. In addition, diabetes education has increased the teachers' participation to the diabetes management.

Oral Session III - New Insulins, Diabetes Treatment and Outcome

O17
Therapeutic value of human vs analogue insulin

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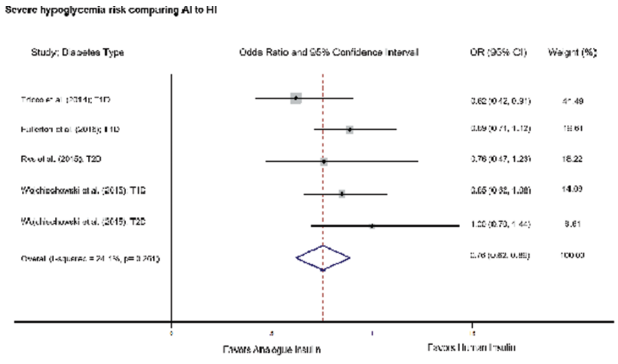
Objectives: In many high-income countries analogue insulins (AIs) dominate the market. However, controversy remains about their benefit relative to human insulin (HI), given their high cost. Therefore, we performed a comprehensive literature review and meta-analysis (MA) to summarize recent data on their clinical benefits.
Methods: Following two recent reviews[1,2] we searched PubMed for studies from 2013-17. Systematic reviews (SRs), MAs and randomized controlled trials (RCTs) comparing HI to AI in ambulatory children and non-pregnant adults with type 1 (T1D) or type 2 (T2D) written in English were included. A limited MA on studies addressing severe hypoglycemia (HypoG) was done.
Results: Of 1,555 records, 23 fulfilled eligibility criteria (7 SRs, 1 MA, 15 RCTs). 11 studies included patients with T1D, 10 with T2D and 2 studies both T1D and T2D. 70% of studies were sponsored by pharmaceutical companies. The MA indicated a benefit of AI reducing severe HypoG (see figure).
Conclusions: Long-acting AIs may reduce the risk of severe HG. There is still no support to recommend AI as first-line therapy, given their high cost, study heterogeneity, and potential conflicts of interest. However, they should be considered in a subset of patients who experience frequent, severe or nocturnal HypoG.

References:
1. Tricco AC et al. BMJ 349: g5459, 2014
2. 18th Expert Committee on the Selection and Use of Essential Medicines, World Health Organization, 2011



[Severe hypoglycemia risk comparing AI to HI]

O18
Randomised, double-blind, crossover trial comparing the safety and efficacy of insulin degludec (IDeg) and insulin glargine U100 (IGlar U100) in young adults with type 1 diabetes (T1D): SWITCH 1 subgroup analysis

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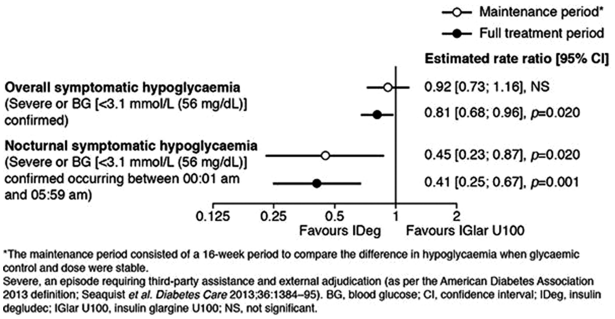
Objective: To compare the rates of hypoglycaemia with IDeg vs. IGlar U100 in young adults with T1D from SWITCH 1 to assess consistency with the overall trial population.
Methods: A *post hoc* analysis of patients (n = 29 [IDeg/IGlar U100 n = 18; IGlar U100/IDeg n = 11]) with T1D aged 18-24 years from SWITCH 1 (64-week, double-blind, crossover, treat-to-target trial; IDeg vs. IGlar U100, both with insulin aspart; n = 501).
Results: At baseline, patients had a mean age of 22.2 years. HbA_{1c} levels, basal insulin doses and body weight were similar for both treatment groups during the trial. Rates of overall (severe or blood glucose-confirmed [<3.1 mmol/L (56 mg/dL)]) symptomatic hypoglycaemia were 23.1 events/patient-years of exposure (PYE) with IDeg and 24.6 events/PYE with IGlar U100 (estimated rate ratio [ERR] 0.92; NS) during the maintenance period and were significantly lower (17.9 vs. 22.5 events/PYE; ERR 0.81; p = 0.020) during the full treatment period. Rates of nocturnal (occurring 00:01-05:59 am) symptomatic hypoglycaemia were significantly lower during the maintenance (2.3 vs. 4.6 events/PYE; ERR 0.45; p = 0.020) and full treatment periods (1.9 vs. 4.4 events/PYE; ERR 0.41; p = 0.001) (Figure). A total of 5 events of severe hypoglycaemia were reported in each treatment arm.
Conclusions: In line with the overall trial population, lower rates of overall and nocturnal hypoglycaemia were observed with IDeg vs. IGlar U100 in a subgroup of young adults with T1D in the SWITCH 1 trial.



*The maintenance period consisted of a 16-week period to compare the difference in hypoglycaemia when glycaemic control and dose were stable.
Severe, an episode requiring third-party assistance and external adjudication (as per the American Diabetes Association 2013 definition; Seaquist *et al. Diabetes Care* 2013;36:1384–95). BG, blood glucose; CI, confidence interval; IDeg, insulin degludec; IGlar U100, insulin glargine U100; NS, not significant.

[Rates of hypoglycaemia (IDeg vs. IGlar U100) in patients with T1D aged 18-24 years from SWITCH 1.]

O19
Efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct to insulin in young adults with poorly controlled type 1 diabetes (JDRF Study; NCT02383940)

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Objectives: Sotagliflozin (SOTA) is a dual SGLT1 and SGLT2 inhibitor in Phase 3 development for type 2 diabetes (T2D) and as adjunct to insulin in type 1 diabetes (T1D). SGLT1 inhibition delays and reduces glucose absorption in the proximal intestine, improving postprandial glycemic control. SGLT2 inhibition reduces renal glucose reabsorption.
Methods: In a double-blind Phase 2 trial of young adults (age 18-30 years) with poorly controlled T1D (A1C ≥9.0%), 87 patients were randomized 1:1 to placebo or SOTA 400 mg once daily for 12 weeks. The primary outcome was change from Baseline in A1C at 12 weeks.

Results: SOTA decreased A1C by 0.35% compared with placebo (p = 0.10). SOTA treatment resulted in lower postprandial glucose (PPG), higher net benefit, lower body weight, and lower A1C in a pre-specified subgroup analysis (9.0% ≤ screening A1C ≤ 10.0%) than placebo (Table). Overall incidences of treatment-emergent adverse events were similar across groups. There were more genital mycotic infections and diarrhea events on SOTA. There was no diabetic ketoacidosis on SOTA.

Conclusion: In young adults with poorly controlled T1D, SOTA for 12 weeks as adjunct therapy to insulin, was well tolerated with evidence of improvements in glycemic control and weight reduction consistent with dual SGLT1 and SGLT2 inhibition.

Efficacy and Safety Results from Randomization to Week 12

	Placebo (n=42)	SOTA 400 mg (n=43)
Efficacy		
A1C at Screening. % (SD)	10.3 (0.95)	10.6 (1.3)
A1C at Baseline. after 2-week screening + 2-week run-in, % (SD)	9.7 (0.93)	9.9 (1.4)
A1C at Week 12, % (SD)	8.7 (1.0)	8.4 (1.5)
A1C at Week 12, LSM Change from Baseline. % (SE. *p<r>-value*[*])	*−0.99 (0.15, <i>p<r><0.001)*	*−1.33 (0.14, <i>p*<0.001)
A1C at Week 12, LSMD vs. placebo[**], % (SE, *p*-value[*])	N/A	−3.5 (0.21, *p*=0.10)
A1C at Week 12, LSMD vs. placebo[**] with 9.0% ≤ screening A1C ≤ 10.0%, % (SE, *p*-value)	N/A	−0.75 (0.26, *p*=0.006)
2-hr PPG LSMD vs. placebo[**], mmol/L (SE, *p*-value[*])	N/A	−3.1 (0.92, *p*=0.001)
Daily CGM time in range 3.9–10.0 mmol/L vs. placebo[*] %(SE, *p*-value[*])	N/A	+7.7 (3.9, *p*=0.057)
Daily CGM time in range 3.9–10.0 mmol/L vs. placebo, hours[†]	N/A	+1.8
Body weight LSMD vs. placebo[**], kg (SE, *p*-value[*])	N/A	−2.4 (0.6, *p*<0.001)
Patients with Safety Events		
Any TEAE, n (%)	26 (61.9)	25 (58.1)
AE as primary reason for early discontinuation of treatment period, n (%)	2 (4.8)	0 (0)
Serious adverse event, n (%)	3 (7.1)	2 (4.7)
DKA, n (%)	1 (2.4)	0 (0)
SH, n (%)	2 (4.8)	1 (2.3)
Nausea[‡], n (%)	3 (7.1)	1 (2.3)
Diarrhea[‡], n (%)	0 (0)	2 (4.7)
Genital mycotic infection[‡], n (%)	0 (0)	2 (4.7)
Efficacy and Safety		
Net benefit [A1C <7.0% at Week 12 and no SH and no DKA Randomization to Week 12]. n (%)	1 (2.4)	7 (16.3)
Net benefit difference, % responders vs. placebo[**], n (*p*-value[*])	N/A	13.9 (*p*=0.026)

[Table]

CGM. continuous glucose monitoring; DKA. diabetic ketoacidosis: LSM. least squares mean; LSMD. least squares mean difference; N/A, not applicable; PPG, postprandial glucose; SD. standard deviation; SE. standard error: SH. severe hypoglycemia; TEAE. treatment-emergent adverse event. [*]Because the primary endpoint was not significant. *p*-values attached to nonprimary/secondary endpoints are descriptive and cannot be used to declare statistical significance. [**]Statistical comparisons of each SOTA arm to placebo were pre-planned and performed using a generalized linear model with repeated measures statistics. [†]Estimated by assuming 100% of daily CGM data available for analysis; therefore, 1.0% of daily CGM time = 0.24 hours. [‡]Mild to moderate with no discontinuations. [¶]Estimated by assuming 100% of daily CGM data available for analysis; therefore, 1.0% of daily CGM time = 0.24 hours.

O20
Metformin improves insulin sensitivity in youth with type 1 diabetes independent of body mass index: a placebo-controlled randomized control trial

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Objective: Cardio-renal disease remains the leading cause of morality in type 1 diabetes (T1D), and relates to insulin resistance (IR). Metformin improves markers of IR (insulin dose and body composition) in obese T1D youth. Yet, little is known about metformin's influence on insulin sensitivity measured by hyperinsulinemic-euglycemic clamp, and its impact in normal weight T1D youth, who like their obese counterparts, display multi-tissue IR despite normal BMI. We hypothesized that metformin would increase insulin sensitivity in both overweight and normal weight participants with T1D.

Methods: Fifty T1D youth ages 12-21 yrs (40% with BMI ≥ the 90% ile) were randomized 1:1 to 3 months of 2000 mg metformin or placebo daily. All youth underwent a DXA scan, fasting labs following overnight intravenous glycemic control, and a multi-stage hyperinsulinemic euglycemic clamp (80 mU/m^2/min insulin). Insulin sensitivity (M/I) is expressed as glucose infusion rate (mg/kg/min) / insulin (uIU/uL).

Results: Compared to the control group, the metformin group experienced improvement in M/I at 80 mU/m^2/min (+12.18±3.16 vs. -2.37±3.64, p = 0.005) adjusting for baseline M/I. Similar results obtained for lean M/I at 80 mU/m^2/min (+18.64±4.81 vs. -3.39±5.55, p = 0.005). The improvement in M/I and lean M/I remained statistically significant after adjusting for sex, pubertal status, BMI %ile and change in HbA1c. Youth with BMI < 90%ile on metformin also experienced a significant increase in M/I (+11.84±4.44 vs. -4.48±4.44, p = 0.02) and lean M/I (+17.61±6.65 vs. -6.95±6.65, p = 0.02), and remained significant after multivariable adjustments.

Conclusions: Metformin therapy improves insulin sensitivity in youth with T1D. The impact of metformin on insulin sensitivity is not limited to overweight T1D youth. IR remains an important risk factor for cardio-renal disease in T1D, and therefore metformin may hold promise as a cardio- and renoprotective intervention.

O21
Dyslipidemia and statin use in adolescents and young adults in the T1D Exchange Clinic Registry

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Objectives: Type 1 diabetes (T1D) and dyslipidemia are risk factors for cardiovascular disease (CVD). We examined dyslipidemia and statin use in T1D Exchange registry participants ages 10-< 25 years with T1D duration ≥1 year, not pregnant, and no CVD.
Methods: Participant characteristics, lipid levels, statin use, and modifiable CVD risk factors of tobacco use, hypertension (HTN), and elevated BMI were extracted from medical charts. Chi-square and t-tests compared characteristics between statin users and non-users and assessed association between meeting LDL target < 100 mg/dL and CVD risk factors among statin nonusers.
Results: The cohort consisted of 6,280 participants (age 16±4 years, 49% female, 78% nonHispanic White, T1D duration 9±4 years). Mean total cholesterol was 170±37, HDL 57±15, LDL 93±31, and triglycerides 109±84 mg/dL. Three percent (n = 158) were on a statin, with mean LDL of 129±40 mg/dL (25% with LDL < 100 mg/dL). For those not on a statin (n = 6,122), mean LDL was 92±30 mg/dL and 64% had LDL < 100 mg/dL. Mean LDL of statin users was significantly higher than nonusers (p< 0.001). Statin use was associated with older age, longer T1D duration, lower income, less frequent blood glucose checks, and HTN (all p< 0.01), but not BMI. HbA1c was higher among statin users than nonusers, even after adjusting for potential confounders (9.8%±2.0% vs. 8.9%±1.7%; p< 0.001). Statin nonusers with LDL ≥100 mg/dL were more likely to have higher BMI and HbA1c compared to statin nonusers with LDL < 100 mg/dL (all p< 0.01).
Conclusions: While the majority of those not on a statin met LDL clinical target, those with LDL above target were more likely to have ≥1 CVD risk factors than those with LDL in target. Only 25% of statin users met LDL clinic target. Based on these findings, longitudinal evaluation of lipid levels and statin use is needed to assess if prompt treatment of dyslipidemia to LDL clinical target in adolescents and young adults with T1D lowers risk for future CVD.

O22
Modest improvement of glycemic control with insulin pump treatment: a population-based prospective cohort study

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Objectives: Insulin pump treatment improves glycemic control. However, little is known concerning the magnitude of this improvement in an unselected pediatric population, controlling for socioeconomic risk factors.
Methods: This prospective cohort study was conducted in the Barbara Davis Center for Diabetes in Denver that follows 84% of Colorado children with T1D. We followed for up to 17 years 3364 Colorado residents diagnosed with T1D < 18 years or age, in 1998-2012. HbA1c levels were measured on average 2.8 x/year, median 20 x/patient. Individual average HbA1c was calculated annually. Linear mixed effects model examined the effect of pump treatment on long-term HbA1c levels adjusting for: age, race/ethnicity, sex, family history of diabetes, health insurance, and the presence of DKA at diagnosis.
Results: Overall, 1315 (39%) of the study participants received insulin pump treatment during the study period. The median duration of pump treatment was 4.3 y [IQR 2.8- 6.4]. Pump initiation < 3 years after diagnosis increased from 4% in 2000-02 to 35% in 2010-12 (p< .0001). Pump treatment was more frequent in older children, first degree relatives of a parent with diabetes and in children covered by private health insurance, compared to those covered by a government-sponsored insurance. HbA1c of pump users tracked 0.4% lower (95%CI 0.3-0.5% p< .0001) compared to children on multiple daily injections. In a mixed effects model, the HbA1c lowering effect of insulin pump treatment was independent of age, sex, and DKA at diagnosis (all p< .0001) as well as ethnic minority status (increased HbA1c by 0.5%, p< .0001), government health insurance (p = .02) or lack of insurance (p< .0001) (both increased HbA1c by 0.2%), and T1D in a first-degree relative (decreased HbA1c by 0.2%, p = 0.01).
Conclusions: Insulin pump treatment in children with type 1 diabetes predicts modestly better long-term glycemic control, independent of demographic factors and access to diabetes care.

O23
The youngest children are the main beneficiary of insulin pump therapy - long-term outcome in children with type 1 diabetes?

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Objectives: The growing popularity of type 1 diabetes (DM1) treatment based on continuous subcutaneous insulin infusion (CSII) raises a question of the group of patients that benefit most from the treatment.
Patients and Methods: Clinical observation was carried out in 285 1-18-year-old patients diagnosed with DM1 treated with CSII. Every 3 months, HbA1c was determined by an agglutination inhibition immunoassay. The patients were followed for 6-10 years.
Results: The greatest benefits from the treatment with CSII using an insulin pump were noted in type 1 diabetes children aged 1-5: the mean HbA1c decreased in these patients from 7,98% to 6,75% (p< 0.01) over 6 years. Slightly lesser outcomes were noted in the group of 6-10-year olds: the mean HbA1c value increased slightly from 7,6% before the CSII to 7,89% after 6 years of treatment (p>0.01). Somewhat worse outcomes were reported in the group of 11-15-year-old children: HbA1c increased from 8,05% to 8,72% (p>0.01). The lowest outcomes were found in the group of the 16-19-year-old patients, as HbA1c rose from 7,8% to 8,82% (p< 0.01) over 6 years. The children receiving the CSII treatment as early as in the first year of treatment exhibited better diabetes control (HbA1c declined from 8,1 % to 7,1% after 6 years, p< 0.01) than patients who received CSII at an older age (HbA1c increased from 7,92% to 8,2%, p< 0.01).
Conclusions: The CSII offers the greatest benefits for patients aged 1-5 and those with the treatment commenced in the first year after diagnosis of type 1 diabetes.

O24
Temporal trends in HbA1c and severe hypoglycaemia rates from 1995 to 2016 for paediatric patients with type 1 diabetes in the DPV and WACDD diabetes registries

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Objectives: To analyse temporal trends in HbA1c and severe hypoglycaemia (SH) rates in paediatric patients with type 1 diabetes (T1D) between 1995 and 2016, using data from the population-based, longitudinal German/Austrian DPV and Western Australia Children's Diabetes Database (WACDD) diabetes registries.

Methods: Paediatric patients diagnosed with T1D aged < 15 years were identified from the DPV (N = 59,857) and WACDD (N = 2,595) diabetes registries and data extracted for all visits dated ≥01/01/1995 and ≤31/12/2016. Patient records were aggregated by calendar year to calculate individual mean HbA1c, total SH events and observation time. Annual mean HbA1c and SH rates were then calculated by registry, sex, age group at time of visit (<6; 6-< 13; 13-< 18 years), insulin regimen (MDI, CSII) and number of visits per year (<2; ≥2; ≥3) based on patients contributing HbA1c/SH values to that year.

Results: The total observation time was 312,222 patient years in both cohorts. Mean age at diagnosis was 10 years, patients attended on average >3 visits/year and mean diabetes duration at end of follow-up was 7 years. Overall, the mean HbA1c was 8.0% (95% CI:7.1 - 8.7) in DPV and 8.4% (95%CI:7.5 - 9.0) in WACDD, with a gradual decrease in both cohorts from 8.3% and 9.2% in 1995 to 7.8% and 8.3% in 2016 respectively. The overall mean SH rate (per 100 patient years) was 3.9 (95%CI:3.8 - 4.0) in DPV and 10.0 (95% CI:9.1 - 10.9) in WACDD, decreasing from 4.8 and 12.0 events/100 patient years in 1995 to 2.0 and 2.8 in 2016 for DPV and WACDD respectively.

Conclusion: Despite a reduction in HbA1c, rates of SH reduced significantly from 1995 to 2016 in both cohorts. A similar pattern of change in glycaemic control and severe hypoglycaemia rates was observed in both genders, across different age groups and insulin regimens.

Oral Session IV - Diabetes Complications

O25

Diabetic ketoacidosis (DKA) at presentation of childhood-onset type 1 diabetes (T1D) in the Nordic countries in 2010-2014 - data from the Danish (DanaKid), Iceland, Norwegian (NCDR) and Swedish (Sweadiabkids) nationwide, childhood diabetes registries

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Objective: DKA is the leading cause of mortality in children with T1D worldwide, associated with increased morbidity and health care expenditure. Our aim is to study the frequency of DKA at onset of T1D and to characterize the variation of DKA over a five-yr period among children < 15 yr in the Nordic countries.
Methods: Data were collected between 2010-2014, from 6,444 children, age 0-14.9 yr, with new onset T1D, registered in 4 nationwide childhood diabetes registries. Data were collected from 85 centres in 4 countries - Denmark (19), Iceland (1), Norway (22), Sweden (43). DKA is defined according to ISPAD; blood glucose>11 mmol/l (200 mg/dL), venous pH< 7.3 or bicarbonate < 15 mmol/l. The severity of DKA is classified as mild (pH< 7.3 or bicarbonate < 1 5 mmol/l), moderate (pH< 7.2 or biocarbonate< 10 mmol/l), severe (pH< 7.1 or biocarbonate< 5 mmol/l).
Results: Altogether 5,855 children had data on DKA at diabetes onset, mean age 8.7 yr (SD3.9), 53.0% boys, 92.3% Nordic ethnicity. 1,248 children (21.3%) had DKA at diabetes onset, mean age 9.0 yr (4.2), 52.4% boys, 87.7% Nordic. Mild DKA was found in 540 children (9.2%), moderate DKA 433 (7.4%), severe DKA 275 (4.7%). Iceland had more children with DKA (33.9%), than Norway (23.5%), Sweden (20.5%), Denmark (20.4%) (p = 0.008). Mild DKA was rather similar in all four countries (range 9.1-10.2) (p = 0.09), but the differences increased with severity of DKA (p< 0.01). Denmark had lowest severe DKA (1.7%) and Norway the highest (7.1%) (p< 0.01). No gender differences for total, moderate and severe DKA, but more boys had mild DKA (p = 0.039). More non-Nordic children had DKA (34% vs. 20%, p< 0.01). In none of the countries the frequency of DKA changed over time.
Conclusions: There are some unexplained country and gender differences in four highly comparable countries that need further exploration. The variation indicates it is possible to reduce the prevalence of DKA, perhaps through increased awareness of diabetic symptoms.

O26

Lower rate of ketoacidosis at diabetes onset, fewer hypoglycemic episodes and more frequent use of insulin pumps in T1D patients with a first-degree relative who already had diabetes - a multicenter DPV study

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Objectives: To determine whether the presence of a first-degree relative with type 1 diabetes (T1D) influences patient treatment and outcome.
Methods: 53,960 T1D patients aged ≥6 months and < 20 y at diabetes onset and with a maximum follow-up period of 10 y were identified from the Diabetes Prospective Follow-up (DPV) database. Of 1,040 individuals with a first-degree relative (parent/sibling/child) with T1D, in 843 diabetes occurred first in a family member, and in 197 the patient had diabetes first. To compare groups, multivariable regression adjusted for age at onset, sex and migration background was used (SAS 9.4).
Results: Age at onset was lowest in patients who had diabetes first (median [IQR]: 6.1 [2.8-9.4] y), followed by patients with a relative who already had diabetes (8.4 [4.7-11.8] y) and highest in patients with sporadic T1D (9.7 [6.0-12.8] y). Sex ratio did not differ. Treatment and outcome one year after onset of T1D with or without a first-degree relative is given in table 1 ([a]p< 0.05 patient first vs. relative first, [b]p< 0.05 patient first vs. sporadic, [c]p< 0.05 relative first vs. sporadic). During follow-up period of 10 y, CSII was used more often in patients having an affected relative, especially if the relative had diabetes first (p< 0.001).
Conclusions: In familial T1D, patients were younger at onset, had better outcome (less DKA at onset, less hypoglycemia during follow-up, lower HbA1c), and more frequently used insulin pumps than patients with sporadic T1D. Differences might be explained in part by the existing knowledge on diabetes and treatment within affected families.

		Familial T1D	
	Sporadic T1D	relative with diabetes first	patient with diabetes first
N	52,920	843	197
Ketoacidosis at onset, %	18.7	8.8[c]	22.9[a]
HbA1c, %	7.58±0.01	7.42±0.06[c]	7.29±0.12[b]
Insulin pump use, %	13.0	26.0[c]	12.5[a]
Severe hypoglycemia, per 100 pat. year	16.0±0.4	8.7±1.7[c]	15.1±5.6

[Table 1: Treatment and outcome 1 year after onset]

O27

Delayed diagnosis of type 1 diabetes in children - still a significant issue?

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Introduction: Same day referral (SDR) for specialist management of suspected type 1 diabetes (T1DM) is widely recommended to minimise rates of diabetic ketoacidosis (DKA) and its associated mortality, morbidity and neurocognitive sequelae.
Objective: The aims of this study were to determine the number of individuals who had attended a general medical professional (GP) prior to presentation for specialist management, to establish the frequency of appropriate SDR practice and the effect of current practice on clinical outcomes.
Methods: Individuals aged ≤18 years diagnosed with new-onset T1DM at two Melbourne tertiary paediatric hospitals (Royal Children's and Monash Children's Hospital) between July 2015 - July 2016 were identified from departmental databases. Data collected included presentation to a GP within 1 month of diagnosis, whether SDR ensued, the time interval between any initial assessment and presentation for specialist review, pre-referral investigations, presence of DKA, length of hospital stay (LOS) and complexity of required care.
Results: During the study period 206 individuals (males = 92) aged 12 months to 17 years diagnosed with new-onset T1DM were identified. Of these 154 (75%) were seen by their GP within the preceding 30 days with SDR in 82/154 (53%). Pre-referral phlebotomy was arranged for 42/154 (27%) individuals. DKA was noted in 93/206 (45%) individuals, and rates were higher in those with delayed referrals (DR) compared to SDR [36/93 (39%) vs 34/93 (37%)]. Severity was increased with DR with more severe DKA (8/93 vs 5/93), worse complications, longer PICU admissions and a difference in LOS compared to SDR (3.7 vs 3.5 days).
Conclusion: The high rates of DKA at presentation and delayed referral indicate a low level of awareness of the symptoms of T1DM and potential risks associated with the delay by GPs. This lends support for a health campaign to improve early diagnosis rates of T1DM.

O28
Prevention of diabetic ketoacidosis in Newfoundland and Labrador, Canada: hospitalization rates pre and post a multiphase provincial knowledge translation study

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Objectives: Newfoundland and Labrador (NL) has one of the highest incidences of Type 1 diabetes mellitus (T1DM) and hospitalizations for diabetic ketoacidosis (DKA). A multiphase, interdisciplinary knowledge translation intervention called the NL DKA project (NLdkaP) aimed to lower rates of DKA hospitalizations.
Methods: NLdkaP occurred from 2011-2012 and included health care professional education on DKA prevention and treatment, a publicity campaign, treatment protocol charts for emergency rooms, and distribution of DKA prevention toolkits to affected families. We measured provincial hospitalization rates of patients (0-24 years) admitted with DKA and diabetes and determined hospitalizations rates and patterns for two years prior (2009-2010), during (2011-2012) and post (2013-2014) NLdkaP. Hospitalization data was collected and maintained by the Newfoundland and Labrador Centre for Health Information (NLCHI).
Results: Hospitalization rates decreased significantly during 2011-2012 compared to 2009-2010; rates increased during 2013-2014 however not to pre-NLdkaP rates. Females had higher rates of hospitalizations for the total group (0-24 years; $p < 0.001$) and in the 10-14 year age group ($p < 0.001$). Hospitalization rates were highest in the 20-24 year age-group ($p < 0.001$).
Conclusions: A multiphase knowledge translation project called NLdkaP was associated with a decreased rate of pediatric DKA hospitalizations during the project. Ongoing education is likely necessary to achieve longer-term reductions in DKA admissions. Females and young adults aged 0-24 years had the highest rates of DKA admissions likely due to psychosocial factors which require targeted interventions to reduce rates in these populations.

O29
Impact of puberty and long term glycaemic control from diabetes onset on incidence of simplex and proliferative retinopathy in type 1 diabetes: the VISS-study

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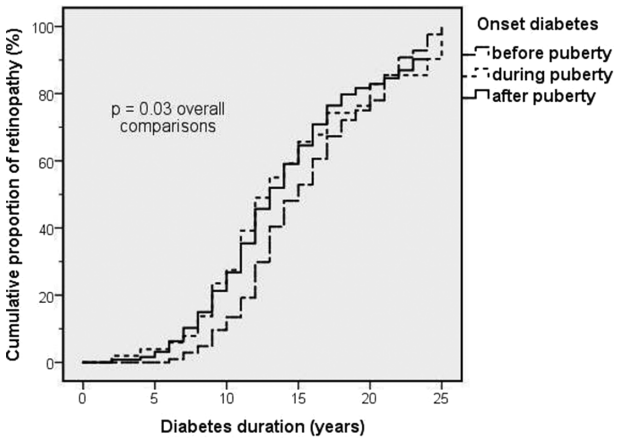
Objective: Glycemic control and diabetes duration are well known risk factors for diabetic retinopathy but there is evidence that the effect of duration is not uniform. Our aim was to evaluate sex, onset in relation to puberty and HbA1c followed from diagnosis and categorized in different time periods as risk factors for developing diabetic simplex and proliferative retinopathy.
Method: An unselected population of 451 patients diagnosed with type 1 diabetes before the age of 35 years during 1983-1987 in the region of South East Sweden was followed. Long term weighted mean HbA1c (wHbA1c) from diagnosis and during the whole follow up of 20 - 25 years was calculated and categorized in different time periods. Retinopathy was evaluated by fundus photography. Life table and Cox regression were used for the analysis.
Result: Onset before puberty was associated with prolonged time to appearance of simplex retinopathy but not of proliferative retinopathy. In Cox regression analysis wHbA1c first 5 years and long term wHbA1c, puberty but not sex were associated with development of simplex retinopathy whereas only long term wHbA1c was associated with proliferative retinopathy.
Conclusion: Diabetes onset before puberty requires longer duration to develop simplex but not proliferative retinopathy. Long term wHbA1c was the most important risk factor for development of proliferative retinopathy whereas wHbA1c during the first 5 years or during different periods of puberty had no influence.



[Incidence of simplex retinopathy and diabetes onset in relation to puberty]

O30
Shared decision making (SDM) approach for diabetes retinopathy (DR) screening for youth with type 1 diabetes mellitus (T1DM): feasibility and perceptions

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Objectives: ISPAD guidelines recommend DR screening begin at age 10 for youth with >2 years T1DM duration, yet adherence is suboptimal. Limited understanding of benefits and risks of DM eye health and DR screening relevance are reported barriers. This study aimed to develop and test a developmentally-appropriate SDM tool to encourage youth with T1DM to make DM self-management decisions related to eye health and screening.
Methods: Literature review and focus groups with DM experts and young adults with T1DM informed development of a SDM tool, which was presented by a DM educator to eligible patients during routine visits. Youth meeting ISPAD screening criteria (n = 113, 41% female, 88% White, mean age 15.5±2.8 y, HbA1c 8.5±1.9%) were randomly assigned to either SDM intervention (n = 59) or served as controls (n = 57); all completed a survey regarding screening attitudes and beliefs.
Results: Regardless of group, worry about T1DM vision loss positively correlated with age (r = .204; p = .03). The SDM group more strongly agreed than control that T1DM affects eye health (4.27±0.8 vs 3.77±1.2; p = .01). The SDM group highly rated the tool, agreeing/strongly agreeing that it helped them to learn that T1DM affects eyes (75%), understand importance of eye exams (86%), feel more comfortable with checks (72%) and improve their interest in their DM care to maintain eye health (88%). 77% of SDM group agreed that the tool should be delivered in practice.
Conclusions: These results demonstrate that a SDM tool designed for youth with T1DM is feasible and offers an opportunity to help them to make informed decisions.about their DM management.

O31
Preclinical retinopathy in type 1 diabetes: screening in pediatric age

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Objectives: Intensive treatment of pediatric T1DM has determined a delayed onset of diabetic retinopathy (DR). DR is still frequently detectable in adults. The aim of our study was to verify the presence of preclinical retinal abnormalities (RA) in pediatric patients with T1DM.
Methods: In the 5-year period between 2011 and 2015, 165 individuals with T1DM were studied for the presence of DR through an ophthalmoscopic examination at the time of the transition from the pediatric to the adult clinics. Median age at the time of the study:19 years. Median T1DM duration: was 9 years. No one showed signs of DR at the time of the transition. Successively, 10% of the patients (16 patients) underwent our study. Two groups were enrolled: one composed of 16 T1DM patients free of any clinical signs of DR and one composed of 15 healthy controls, of comparable age. Both groups underwent a eye examination, an OCT (Optical Coherence Tomography) and DVA (Dynamic Vessel Analyzer) of the left eye. Presence of DR at baseline implied the exclusion from the study.
Results: 2/16 T1DM patients were excluded from the study due to signs of diabetic retinopathy at baseline. Seven were diagnosed with retinal dysfunctions (identified by OCT and/or DVA) potentially related to the preclinical stage of DR. The 7 patients with preclinical RA had a longer duration of T1DM when compared to diabetic patients without retinal dysfunctions (14.1 ± 2.9 vs 10.0 ± 1.7, years ± SD, p = 0.007). The retinal dysfunctions found in these patients consisted in the thinning of the retinal nerve fiber layer identified by OCT, and a reduced myogenic response (reduced arterial dilation) identified by DVA.
Conclusions: These data confirm the necessity to investigate for the presence of preclinical DR in subjects with a long duration of T1DM. Prospective studies are necessary to verify whether the early RA identified through the above described techniques (OCT and DVA) are truly due to DR in the preclinical stage.

O32
Once may be enough: screening eye exams in youth with T1D < 18 years of age

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Objectives: While ADA guidelines indicate that youth with T1D >10 yrs of age and 3-5 yrs duration should have annual eye exams, a number of studies suggest that treatable retinopathy is rare in youth with T1D prior to 18 yrs of age. We evaluated this question in Diabetes Control and Complications Trial (DCCT) participants age 18 yrs or younger, who had at most minimal to moderate non-proliferative retinopathy at baseline.
Methods: Standardized stereoscopic 7-field fundus photographs were obtained every 6 months during DCCT (1983-92). Photographs were graded centrally using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. Transitions in retinopathy status over time were reviewed.
Results: 195 participants (102 in the conventional group and 93 in the intensive group) contributed 1031 retinopathy assessments while they were still under 18 yrs and over 2.3 yrs of mean follow-up. No one developed severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) and 1 participant (intensive group, female) reached clinically significant macular edema (CSME) while less than 18 yrs (Table). In this incident case, baseline risk factors included diabetes duration 9.3 yrs, HbA1c 10.3%, LDL 131 mg/dl, and mild retinopathy (35/35 ETDRS scale).

From/To	No DR	Mild NPDR	Mod. NPDR	Severe NPDR	PDR	CSME
1. No DR	393	105	1	0	0	0
2. Mild NPDR	83	230	9	0	0	1
3. Mod. NPDR	0	9	3	0	0	0
4. Severe NPDR	0	0	0	0	0	0

[Between visit transitions in retinopathy status]

Conclusions: Youth with T1D are highly unlikely to develop treatable retinal lesions prior to 18 yrs of age if their initial screening exam shows no or mild NPDR.

Oral Session V - Epidemiology

O33

Fr1dolin: Pediatric population screening for type 1 diabetes (T1D) and familial hypercholesterolemia (FH) in Lower Saxony, Germany

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Objectives: To prove the feasibility of a combined screening for presymptomatic T1D and FH in children living in the State of Lower Saxony, Germany. Screening for T1D has already been successfully started in the German Federal State of Bavaria with the Fr1da-Project which plays a pioneering role for the Fr1dolin-Study.
Study design: Population-based screening in children aged 2 to 6 years during the compulsory routine check-ups at the pediatrician's office and standardized follow-up of affected children in specialized centers.
Methods: Capillary blood sampling for detection of T1D-associated antibodies (IAA, GADA, IA-2A, ZnT8A; Helmholtz Diabetes Center, Munich) and LDL cholesterol (LDL-C) measurement (Children's Hospital AUF DER BULT, Hannover) as well as collection of disease specific family history using a questionnaire. In case of a positive result, a second blood sample is taken and if diagnosis is confirmed, disease specific counseling and support of the family are organized. Potential psychological burden of the parents is evaluated (Medical Psychology, Hannover Medical School). Follow-up examinations are planned until the age of 12 years or up to 6 months after the clinical onset of T1D.
Interim Results: Currently (May 15, 2017), 1,691 children (52.4% boys; age: 4.0±1.2 years; mother's age: 34.7±5.6 years; father's age: 37.8±6.8 years; mean±SD) have been screened. In 61 (3.6%) participants, laboratory examinations could not be done because of insufficient sample volume or total hemolysis. 79/1,630 (4.8%) children presented elevated LDL-C (≥135 mg/dl), 5/1,293 (0.39%) showed multiple T1D-antibodies. In 17/34 (50.0%) children elevated LDL-C and in 1/1 child (100%) multiple T1D-antibodies were confirmed in a duplicate analysis so far.
Conclusion: The first results of the Fr1dolin Screening show an estimated prevalence for presymptomatic T1D (approx. 1:300), but significant higher prevalence for FH than expected (approx. 1:200) in general population.

O34

Development of islet autoimmunity and type 1 diabetes in twins and siblings

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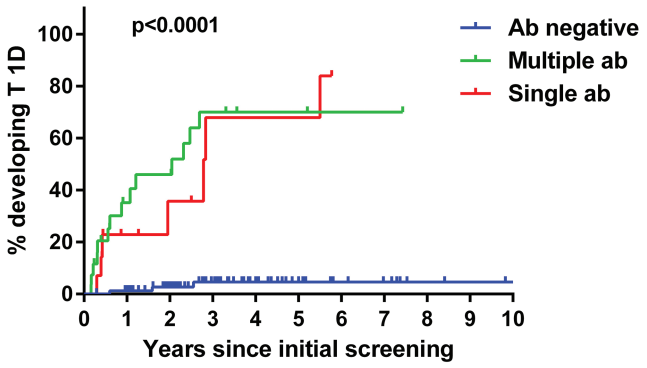
Objective: Identical twins (IT) have a high risk of concordance to progression of autoantibodies (Ab) and type 1 diabetes (T1D) after one twin is diagnosed. We examined the development of Ab and T1D over time in self-reported IT, non-identical twins (NT) and full siblings (FS).
Methods: A total of 13292 unaffected siblings were screened in the TrialNet Pathway to Prevention Study between 2004-2015. Ab results for GAD65 (GADA), ICA512 (IA2A), and insulin (IAA) were available over time for 8387 participants: 90 IT, 118 NT and 8179 FS (median age at screening 9 yrs, median follow-up 2 yrs).
Results: Development of IAA was highest in IT (34%) compared to 21% in NT (p = 0.03) and 15% in FS (p = 0.06 NT vs FS). Development of GADA and IA2A were higher in IT (49% and 29%) compared to NT (18% and 14%) and FS (18% and 12%) (p< 0.0001). When stratified by Ab status at screening, survival analysis was significantly different by sibling type. IT had ~70% risk of developing T1D by 3 years for both single and multiple Ab compared to 5% for Ab negative subjects (Figure). The 3 year T1D risk for NT was 73% for multiple Ab, 8% for single Ab and < 1% for Ab negative. FS had a 3 year T1D risk of 47% for multiple Ab, 11% for single Ab and < 1% for Ab negative subjects.
Conclusion: IT have a higher risk of developing Ab and once positive for ≥1Ab a faster progression to T1D. NT have an intermediate risk with multiple Ab NT having a T1D risk similar to IT, while single Ab NT have a risk similar to FS.



[Figure]

O35

Improvement of diabetes control in Czech children: data from the National Childhood Diabetes Register ČENDA

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Objectives: The Czech National Childhood Diabetes Register (ČENDA) is a web-based national database that stores treatment and outcome data in children and adolescents with diabetes (DM), allowing for anonymous comparison among diabetes clinics. Here we present data from the first four years (2013-2016).
Methods: Since 2013, the database collects data on every patient treated by 48 participating pediatric diabetes outpatient clinics. Data

include characteristics of the disease onset, and annual summaries of key clinical care parameters, including every available HbA1c value.
Results: In 2016, the database contains data of 3030 children which is estimated to be 80% of all Czech pediatric DM patients. Of these, 95% had type 1 diabetes (T1D), 4% had genetically proven monogenic or other type of DM, 1% had type 2 diabetes. These proportions remained stable over the 4 years of follow-up. In children with T1D, median HbA1c was decreasing throughout the observed period: 66.3 - 65.2 - 64.0 - 62.6 mmol/mol for years 2013 - 2016. Consequently, the proportion of children reaching target therapeutic goal of 58.5 mmol/mol increased from 27% in 2013 to 35% in 2016. This improvement was significant in all categories of age and diabetes duration. Out of children treated by insulin, 75% were on multiple daily injections (MDI), 24% on continuous subcutaneous insulin infusion (CSII) and 1% on conventional therapy. This ratio remained unchanged over the last four years, but we observed a significant increase in the proportion of preschool children treated by CSII (from 7 to 21%). Main predictors of low HbA1c were mode of treatment (CSII), gender (male) and size of the center (large).
Conclusions: ČENDA database provides longitudinal national-wide data on pediatric diabetes control. We present a significant decrease in HbA1c over the last four years that was not linked to an increase in proportion of children treated with CSII.

O36
The clinician factor: personality characteristics of clinicians and their impact upon clinical outcomes in the management of children and adolescents with type 1 diabetes

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Objectives: Previous studies have identified idiosyncratic clinician qualities that have had a seemingly disproportionately positive impact on outcomes. The purpose of this study was to investigate these qualities in a systematic manner.
Methods: To isolate clinician qualities from other aspects of care, we exploited the context of several clinicians caring for randomly allocated patients, within the same tertiary care setting. All youth with T1D who had seen the same clinician exclusively over the previous year were included; data were collected prospectively over a 3 month period.

The primary outcome measure was clinician mean HbA1C, controlling for patient number, age, gender, duration of diabetes, insulin regimen and rates of severe hypoglycaemia. Clinicians completed a questionnaire assessing goals for blood glucose levels and HbA1C, the Diabetes Attitude Scale and Attitude and the Big Five Personality Inventory questionnaire.
Results: 719 youth seen by eight clinicians were included. Between clinicians there were no significant differences in patient characteristics, insulin regimens, glycaemic goals or clinician personality inventory scores. There was a significant effect ($F = 2.36$; $df = 7$; $p = .022$) of treating physician on mean HbA1c, ranging from 7.7% to 8.3%. Treating physicians who strongly agreed that "almost everyone should do whatever it takes to keep their blood sugar close to normal" and strongly agreed that "health care professionals should help children and parents make informed choices about their care plans", had the lowest mean HbA1c outcomes. After controlling for these two items, the effect of treating physician on HbA1c was no longer significant.
Conclusions: Within one large tertiary diabetes clinic there was considerable variation between clinical outcomes despite a homogenous care delivery and no patient selection bias. The determining variables of clinical outcomes between clinicians were strong directive and outcome orientated attitudes.

O37
The outpatient clinic visit in mind and reality

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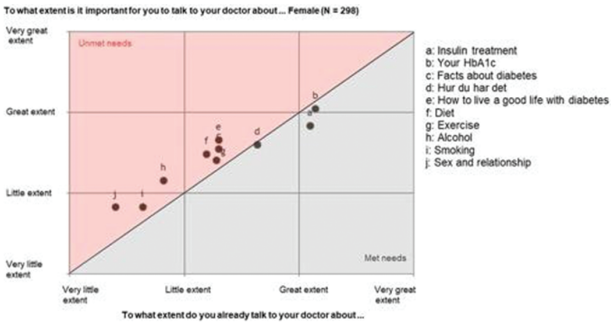
Objective: To investigate the teenagers´ view on important topics for conversation compared to what teenagers believed had been discussed with the diabetes nurse and the pediatric diabetologist at the outpatient clinic visit.
Method: In the national TODS (Teenagers on Diabetes Sweden) study, all adolescents with type 1 diabetes in Sweden in ages 15-17.99 years (N = 2112) were sent an invitation to complete an online questionnaire on different aspects on living with diabetes. One part of the form dealt with the meeting at the outpatient clinic.
Results: The adolescents of both sexes scored the importance of discussing the insulin treatment and the HbA1c value as very high and that these needs where met. Males (N = 155) expressed unmet needs to discuss sexuality and use of alcohol. Females (N = 298) thought that "how to live a good life with diabetes" is important to discuss and should be accentuated. Females also wanted more dialogue on issues as exercise and nutrition and expressed unmet needs in discussions on alcohol, sex and smoking.
Conclusion: Consensual agreement on important areas to discuss on the life with diabetes is essential for a fruitful cooperation between the adolescent and the professional team members. An individual checklist on important topics of conversation could simplify and improve the communication skills.



[ ]

O38
Centre size may influence HbA_{1c} - an international study

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Objective: The variance in glycemic control among childhood diabetes centres is not fully understood. This study aims to investigate the association between centre size and glycemic control in children with type 1 diabetes (T1D).
Methods: Data were collected between 2013 and 2014 from 57,950 children < 18 years with T1D; 54,494 with complete data on HbA_{1c} and covariates. Data were collected from 504 centres in seven countries - Austria (19), Denmark (19), England (163), Germany (219), Norway (27), Sweden (43), and Wales (14). The centre sizes were grouped as follows: Group 1: ≤ 20 patients, group 2: > 20 and ≤ 50 patients, group 3: > 50 and ≤ 100 patients, group 4: > 100 and ≤ 200 patients, group 5: > 200 patients. Mean HbA_{1c} was compared between groups before and after adjusting for the covariates: sex, age, diabetes duration and minority status, before and after stratifying for treatment modality (injection/pump). Analysis was performed by the statistical package SAS 9.4.
Results: Forty-eight centers (9.5%) had less than 20 patients (362 patients (0.7%)), and 69 centres (13.7%) had more than 20 and less than 50 patients (2,274 patients (4.2%)). The small centres were concentrated in Austria, Germany and Norway. Crude mean HbA_{1c} per group was significantly higher in the groups with less than 50 patients (P< 0.001). Mean HbA_{1c} per group adjusted for covariates was: Group 1: 70.5 mmol/mol, group 2: 66.8 mmol/mol, group 3: 65.0 mmol/mol, group 4: 65.2 mmol/mol and group 5: 65.0 mmol/mol, still significantly higher in the groups with less than 50 patient (P < 0.001). Stratifying by treatment modality did not change this result.
Conclusion: The percentage of patients treated in small centers differed between countries. In all countries combined, childhood diabetes centres with less than 50 patients tended to have higher HbA1c, but this finding was not universal for all countries. This may reflect differences in topography and clinical practices between countries.

O39
Glycaemic targets how low can you go? An in-depth exploration of clinician beliefs and attitudes to glycaemic target setting

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Objectives: The majority of Australian children and adolescents with type 1 diabetes do not meet HbA1c targets endorsed by guidelines (Phelan, 2017). This has implications for future risk of diabetes complications. Evidence suggests clinician attitudes and beliefs about glycaemic targets influence patient outcomes, however the literature on target setting in childhood diabetes is scant. (Swift, 2010) The aim of the study was to investigate and describe clinician experience and approach to glycaemic targets.
Methods: This qualitative study, informed by grounded theory (Strauss, 1994) used purposive sampling to invite participants from a diabetes team where the NICE target for HbA1c of < 48 mmol/mol (NICE, 2015) has been adopted. Participants were individually interviewed by one of two researchers using a semi-structured interview schedule. The interviews were recorded and transcribed, with two researchers independently coding the transcripts, applying the agreed codes to each transcript, arranging the data into files based on the identified codes and examining each file for themes.
Results: Eight diabetes health care professionals were recruited to the study and interviewed. Broad recurring themes arising from the preliminary analysis of the transcripts include 'Target as an unwritten law', 'normal in every way is the goal', 'Evidence-what it tells us', 'Celebrate the wins', ' and the 'Central role of family, routine and habit'.
Conclusions: From this preliminary analysis we have described beliefs and attitudes common to a team of healthcare professionals who consider the NICE recommendation as an achievable target for their clinic. This provides insight into one teams approach to tightening of glycaemic targets. Further research including health care professionals where this target has not been adopted is required to understand the perceived barriers to tightening glycaemic control and how this translates into clinical care and management.

O40
International benchmarking in type 1 diabetes: HbA1c increases equally with age, independent of HbA1c at younger age

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University of Gothenburg, Department of Paediatrics, NU Hospital Group, Gothenburg, Sweden, [23]Children's Hospital for Wales, on behalf of the National Paediatric Diabetes Audit (NPDA) and the Research and Policy Division of the Royal College of Paediatrics and Child Health, Department of Paediatric Endocrinology and Diabetes, Cardiff, United Kingdom

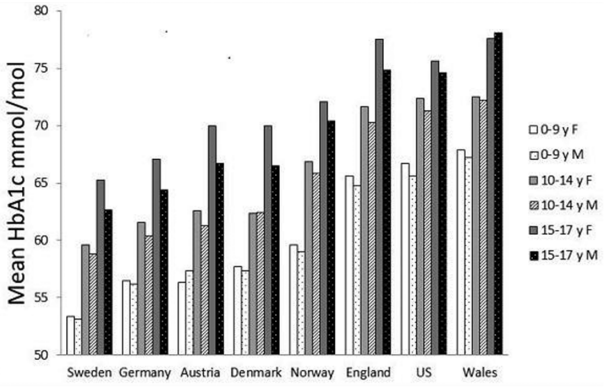
Objectives: There is a considerable difference in mean HbA1c between countries. Can this be explained by differences between age groups and/or gender?

Methods: Data on HbA1c during 2013/14 from 66,071 children < 18 years with type 1 diabetes in eight developed western countries were analysed. Austria (n = 1,583), Germany (n = 20,187), Denmark (n = 1,894), England (n = 21,401), Wales (n = 1,284), Norway (n = 2,321), Sweden (n = 6,524) and USA (n = 10,877). Last available HbA1c and age were included.

Results: Within each country, HbA1c was positively associated with increasing age group ($p < 0.001$), independent of the HbA1c within the younger age group. The pattern was the same in all countries (Fig 1). The increase in mean HbA1c between age group 0-9 yr and 15-17 yr varied between 9.0 mmol/mol in USA and 11.9 in Norway, an inter country difference of 2.9 mmol/mol.

The maximum difference in mean HbA1c between genders within each country was 1.6 mmol/mol (England). In the age groups 0-9 and 10-14, the mean HbA1c differences were smaller, while in age group 15-17 girls had higher HbA1c in all countries except Wales.

Conclusions: The difference in mean HbA1c between countries could not be explained by age, as the pattern with a pre-pubertal increase and further deterioration during puberty is independent of the country of origin, despite different mean HbA1c levels in the countries. The gender difference in mean HbA1c was most pronounced in the 15-17 yr group, and similar in most countries.



[Fig.1]

Oral Session VI - Technology

O41

Long-term study of a tubeless insulin pump vs. multiple daily injections in youth with type 1 diabetes: data from the German/Austrian DPV-Registry

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Objective: The purpose of this study was to examine the glycemic control in youth with type 1 diabetes who switched from multiple daily injections (MDI) to a tubeless insulin pump (Omnipod® Insulin Management System, Insulet Corp., Billerica, MA) compared to those patients who continued MDI therapy over a 3 year time period.
Research design and Methods: This retrospective analysis of the German/Austrian Diabetes Patienten Verlaufsdokumentation (DPV) registry included data from 458 centers and 2529 patients < 20 years (n = 660 tubeless insulin pump; n = 1,869 MDI) who initiated treatment on the tubeless insulin pump as of January 1, 2013 and had 1 year of data pre-, 2 and 3 years of data post-treatment switch from MDI. Only patients from experienced centers (>10 Patients with Omnipod) were included. For comparison, all MDI patients from same centres in the same period were used. Outcomes included the change in HbA1c, insulin dose and body mass index (BMI) standard deviation score (SDS).
Results: In this 3-year, retrospective analysis of youth with type 1 diabetes who switched from MDI therapy to a tubeless insulin pump showed better glycemic control at 1 year compared to patients who continued MDI treatment, (7.52%±0.03 vs. 7.68%±0.02; p< 0.001) with no between group difference at 2- and 3-years. Total daily insulin dose was lower in the tubeless insulin pump group, 0.80±0.01, 0.81±0.01 and 0.85±0.01 U/kg/24 h vs. the MDI group, 0.89±0.01, 0.94±0.01 and 0.97±0.01 U/kg/24 h, at 1-, 2- and 3-years, respectively (all p< 0.001). BMI (SDS) increased in both groups and was not different at 1-, 2- and 3-years.
Conclusions: Treatment with a tubeless insulin pump in youth with type 1 diabetes was associated with significant improvements in glycemic control in the first year and daily insulin need compared with MDI and appears as an effective alternative to MDI in youth with type 1 diabetes.

O42

Continuous glucose monitoring (CGM) and glycemic control among youth with type 1 diabetes (T1D): international comparison from the T1D exchange (T1DX) and the DPV initiative

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Objectives: To assess change in rates of pediatric CGM use over the past 5 years, and how it impacts glycemic control, data from 2 registries were compared: the US-based T1DX and the German/Austrian DPV.
Methods: Registry participants aged < 18 yrs with T1D duration ≥ 1 yr encompassed 29,003 individuals in 2011 and 29,124 participants in 2016. Demographic data, CGM use and A1c were obtained from medical records.
Results: CGM use increased in all age groups in both registries, and was most pronounced in the youngest patients (Table). In 2011, CGM use did not alter A1c in DPV participants (7.8% vs 7.9%, p = 0.26); yet, in 2016, A1c was lower in CGM users (7.5% v 7.9%, P< 0.001). For T1DX CGM users, lower A1c was seen in both 2011 (7.9% v 8.6%, P< 0.001) and 2016 (8.1% v 9.0%, P< 0.001). In 2016 mean A1c was lower among CGM users regardless of insulin delivery method compared to pump only (P< 0.001) and injection only (P< 0.001) in both T1DX and DPV registries. In 2016, CGM users were more likely to achieve glycemic targets (A1c < 7.5%) for DPV (58.1% v 42.9%, P< 0.001) and T1DX (32.3% v 14.6%, P< 0.001).
Conclusions: Pediatric CGM use increased in both registries and was associated with improved glycemic control regardless of insulin delivery modality. As penetrance of this technology is lowest in adolescents, a group noted to have the highest mean A1c, strategies to engage this cohort of youth in adoption and long-term use of CGM are needed.

Table: Percent CGM Use for DPV and TIDX Registry Participants and Glycemic Control in 2016

	DPV		TIDX	
	2011 N=17,395 % CGM Use	2016 N=20,938 % CGM Use	2011 N=11,608 % CGM Use	2016 N=8,186 % CGM Use
Overall	3.6%	18.4%	3.2%	21.7%
Age Group				
<6 years	6.0%	28.2%	4.4%	44.5%
6-<12 years	3.6%	22.3%	3.6%	26.8%
12-<18 years	3.4%	15.7%	2.6%	16.5%
Insulin Delivery Method				
Injections	2.6%	13.6%	0.6%	8.5%
Pump	5.0%	22.2%	5.2%	29.2%

	DPV		TIDX	
Glycemic control	**N**	**Mean AIC in 2016**	**N**	**Mean Alc in 2016**
CGM+pump	2595	7.5%	1456	8.0%
CGM+injection	1245	7.6%	241	8.2%
Pump alone	9030	7.8%	3503	8.8%
Injection alone	7838	8.0%	2565	9.3%

[Table]

O43
Closed-loop outperforms threshold-low-glucose suspend insulin delivery on glucose control in pre-pubertal outpatients with type 1 diabetes

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Glucose excursions result in deleterious brain outcomes and impaired quality of life in children with type 1 diabetes (T1D).

Our randomized cross-over outpatient study compared glucose control with closed-loop (CL) vs. threshold-low-glucose suspend (TLGS) insulin delivery (ID) in pre-pubertal T1D children. The ID system included Dexcom G4 Share continuous glucose monitoring (CGM), Tandem t:slim insulin pump and DiAs control platform (Virginia University) to which CGM and pump were wirelessly connected and which run alternatively a model predictive control/control to range or a TLGS algorithm with CGM glucose alarm threshold at 70 mg/dl resulting in insulin infusion stop for 2 hours in case of missed alarm. Glucose control was assessed from CGM data. The children (n = 24, 14M/10F, age (mean, range): 9.4 (7-12) yrs, A1c: 7.5±0.5%, pump use since 5.2±3.1 yrs) and their parents were admitted on Day 1 at 17:00 in a hotel for two 3-day sessions at 3-4-week interval. ID system was installed at admission time and CL or TLGS were initiated at 8:00 on Day 2 for 48 hours. Free meals were taken at 9:00, 13:00 and 20:00 and a free snack at 17:00; meal boluses were managed according to individual ins/carb ratios. Free physical exercise occurred after breakfast and lunch. Night sleep was from 22:00 to 8:00.

Percent time spent with CGM in 70-180 mg/dl and 70-140 mg/dl ranges and mean CGM level during the 2 consecutive nights (22:00-8:00) were significantly better with CL vs. TLGS: 67 vs. 41%, 42 vs. 20% and 162 vs. 192 mg/dl, respectively (all p< 0.001), while % time with CGM< 70 mg/dl was lower: 0.9 vs. 1.3 albeit not significantly. Over 48 hours, the same indices were also better in CL: 64 vs. 48%, 39 vs. 28% and 160 vs. 180 mg/dl, respectively (all p< 0.001).

Our data shows a better glucose control can be obtained with CL vs. TLGS ID in still poorly investigated pre-pubertal T1D outpatients. Confirmation on longer duration would have a valuable positive impact for T1D children.

O44
Optimal predictive low glucose management settings during physical exercise

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Objectives: To assess the optimal setting of the predictive low glucose management (PLGM) algorithm for preventing exercise-induced hypoglycemia in adolescents with type 1 diabetes.
Methods: Thirty-four adolescents, 15-20 y, wearing PLGM system, were followed during 3 days exercise in free-living conditions. PLGM threshold was set at 70 mg/dl between 8 am-10 pm and 90 mg/dl during 10 pm-8 am. Adolescents were divided in group A and B, with PLGM threshold at 90 and 70 mg/dl, respectively during exercise. Time spent in hypoglycemia and AUC for time slots 8 am-1 pm, 1 pm-4 pm, 4 pm-11 pm, 11 pm-3 am, 3 am-8 am, in 3 days were compared between groups by Wilcoxon rank sum test.
Results: We analyzed 31 patients (median age 15.0 y, 58.1% males, median diabetes duration 7.0 y, HbA1c 7.1%). No significant difference has been observed in time spent in hypoglycemia between groups using threshold 70 or 90 (table). Time spent in target was similar in both groups, as well as time spent in hypo or hyperglycemia. The trends of blood glucose over the three days in the 2 groups overlapped without significant differences.
Conclusions: A PLGM threshold of 90 mg/dl during the night was associated with reduced time in hypoglycemia in adolescents doing frequent physical exercise, while maintaining 65.1% time in range. However a threshold of 70 mg/dl seems to be safe in the duration of the physical exercise. PLGM system in adolescents with type 1 diabetes was effective to prevent hypoglycemia during and after exercise, irrespective of the PLGM thresholds used.

Time (%)	All (n = 31)	Group A (n = 18)	Group B (n = 13)	p
<50 mg/dl	0 (0; 0.2)	0 (0; 0.1)	0 (0; 0.2)	0.923
<54 mg/dl	0 (0; 0.5)	0.1 (0; 0.4)	0 (0; 0.6)	0.546
<70 mg/dl	2.3 (0.3; 4.3)	1.8 (0.3; 4.5)	2.3 (0.5; 3.9)	0.920
70-180 mg/dl	65.1 (53.7; 72.6)	64 (51; 71.9)	65.1 (59.6; 73.4)	0.423
>180 mg/dl	35 (22.6; 43.2)	35.4 (24.7; 47.6)	35 (19.4; 38.5)	0.401

Values are expressed as median (1st; 3rd quartiles); p-values refer to Wilcoxon rank test

[Glycemic control during physical exercise]

O45
Day-and-night use of smartguard technology versus open-source hybrid closed-loop OpenAPS in extreme sports conditions

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Objectives: Our aim was to assess safety, feasibility and efficacy of open-source hybrid closed-loop (OpenAPS) compared with predictive low-glucose management (PLGM) alone in day-and-night glucose control in extreme conditions.
Methods: A total of 22 children (16 girls, aged 6-15 years, average HbA1c 57±8) were enrolled to a pivotal winter sports camp study. All children were divided between two groups for three consecutive nights and days, the first with PLGM (n = 12, Minimed® 640G pump, sensor Enlite™) and the latter with open-source hybrid closed-loop OpenAPS (DANA Diabecare R pump, sensor Dexcom G4™, software OpenAPS). The PLGM was set to 3.2 mmol/l during nighttime and 3.4 mmol/l during daytime. The OpenAPS was set to 6 mmol/l for the whole day. Hypoglycemias were treated with dextrosis with the respect to levels and trends of glycemia. Physical exertion was represented by all day alpine skiing. Primary endpoints were as follows: time spent below the threshold of 3.9 mmol/l, time spent within the target range of 3.9 to 7.8 mmol/l and mean glucose level.
Results: Compared to the PLGM group, the OpenAPS group had significantly lower mean glycemia levels (median 6.9±0.6 vs 7.5±0.9 mmol/l,

p< 0.05). The proportion of time spent below the target (mean 4.3±2.4 vs 4.3±2.9%) and in the target zone (64±8 vs 55±16%) was not significantly different. The time spent in target zone in the OpenAPS group was affected by more frequent malfunctions of the cannula set (1.5±0.05 vs 0.4±0.5, p< 0.01). No significant difference was found in the amount of carbohydrates consumed for the prevention and treatment of hypoglycemia (38±28 vs 38±14 grams). No episodes of severe hypoglycemia or other serious adverse events were noted.
Conclusion: Both SmartGuard and OpenAPS systems are safe and effective in preventing hypoglycemia in extreme sports conditions. However, better glycemia control was achieved with OpenAPS.

O46
The freestyle flash glucose monitoring system has limited effect on the metabolic control of children and adolescents with type 1 diabetes mellitus

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Background and aims: The FreeStyle® Libre Flash Glucose Monitoring System (FSLFGMS, Abbott) measures glucose concentrations in the interstitial fluid for up to 14 days. Limited data exist on the effect of FSLFGMS on the metabolic control in children and adolescents. We evaluated the short term (3 months) and middle long term (8 months) effect of FSLFGMS on the HbA1c.
Methods: 78 children with type 1 DM (39 boys), aged 4.7-17.6 yrs were included. All patients had at least 6 months DM: 27 were treated by insulin pump and 52 by multiple daily injections. They started FSLFGMS between June 1 and October 31, 2016. The HbA1c nearest to the date of FSLFGMS start (T0) was compared with the HbA1c after 3 months (T3) and after 8 months (T8) of sensor wear. 3 groups were made according to the initial HbA1c: group 1: HbA1c < 7.5%; group 2: HbA1c 7.5-8.4%; group 3: HbA1c ≥8;5%. After 6 months of FSLFGMS the patients and their caregivers were asked to fill in a questionnaire on the usability for the FSLGFMS.
Results: 6 patients discontinued early FSLFGMS (4 discomfort, 1 allergic skin reaction,1 discordance between capillary glucose measurements and FSLFGMS reading). The 72 subjects that continued FSLFGMS were very satisfied with the FSLFGMS. Mean (SD) HbA1c (%) for the 3 groups at different time points are shown in the Table.

	T0	T3	T8
All	7.7 (1.1)	7.5 (1.0)a	7.9 (0.9)b,c
Group 1 (n = 34)	6.8 (0.6)	6.8 (0.5)	7.3 (0.5)c,d
Group 2 (n = 20)	8.0 (0.3)	7.8 (0.7)	8.2 (0.7)e
Group 3 (n = 18)	9.2 (0.7)	8.7 (1.0)a	8.9 (0.8)

[Results]
[a] p< 0.05 T3 vs T0; [b] p< 0.05 T8 vs T0; [c] p< 0.001 T8 vs T3; [d] p< 0.001 T8 vs T0; [e] p< 002 T8 vs T3.

Conclusion: In patients with a HbA1 < 8.5% FSLFGMS did not improve metabolic control. In contrast, HbA1c after 8 months of FSLFGMS use was higher than at start. In patients with a HbA1c ≥8,5% FSLFGMS improved slightly the HbA1c. Further studies are imperative in order to optimize the use of the FSLFGMS in children.

O47
Is insulin pump therapy associated with longer-term improvement in behaviour, mood, cognition and glycaemia in children and adolescents with type 1 diabetes?

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Objectives: We have previously reported improvements in HbA1c & behaviour four months (4 mo) after commencing continuous subcutaneous insulin infusion (CSII) as compared with continued use of multiple daily injections (MDI) in a randomised controlled trial (RCT) of 101 youth with Type 1 diabetes. This study examined whether improvements seen with CSII at 4 mo were sustained longer term.
Methods: A prospectively planned follow-up study was conducted 2 yr (±6 mo) from enrolment. As per protocol, MDI-users had commenced CSII at the end of the 4 mo RCT comparison period. Assessments of the following measures (also conducted at baseline & 4 mo) were obtained: behaviour and mood (Behavior Assessment Schedule for Children [BASC-2]), executive function (Behavior Rating Inventory of Executive Function [BRIEF]) and glycaemia (HbA_{1c} -Bio-Rad D-10TM HPLC).
Results: Data at 2 yrs were available for N = 76/101 (75%). Fifteen (19.7%) were no longer using CSII, hence n = 61 had paired data from baseline (pre CSII) to +2 yrs of CSII. Preliminary analyses using paired t tests showed no difference in HbA1c (7.7% vs 7.8%, p = 0.68), adaptive skills (p = 0.15), or parent-reported total (p = 0.25), externalising (p = 0.31), or internalising (p= 0.18) behaviours with CSII use to 2 yrs. Executive skills were significantly better at +2 yr compared to baseline (mean[SD] BRIEF score 53.7 [9.7] vs 50.9 [13.2], p = 0.02), as they had been in this subgroup at 4 mo (p = 0.001)
Conclusions: Previously documented improvements in HbA1c & behaviour after 4 mo of CSII use appear short-lived. The only sustained benefit of CSII use at 2 yr relative to baseline was in executive function, where small improvements (0.29 SD) were seen. Executive function has previously been associated with improved diabetes management, however sustained improvement in HbA_{1c} was not evident here. These data highlight the importance of repeated assessments of outcomes when evaluating the impact of diabetes-related technologies.

O48
Continuous glucose monitoring in children and young person with diabetes: is it a way forward?

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Objective: The Families with Diabetes National Network (FWD NN) is a parents' reference group for the National Children/Young People's Diabetes Network with the aim of providing a forum for communication between the network and the parents of children with diabetes and supporting the development of a National Diabetes Service Improvement Delivery Plan for children.

Background and Methods: UK NICE guidelines 2016 established the criteria for the use of a Continuous Glucose Monitoring (CGM) in children to help with the management of their diabetes. But there is no agreed one pathway on how to secure appropriate funding from service providers.

FWD NN conducted a survey to ascertain children with diabetes' & their families' experience of CGMs.

Results: Number of respondents were 593.

- 78% had seen a reduction in Hba1c since using CGM
- 96% agreed that a CGM had allowed their child to be more independent
- 98% felt that having a CGM had given them the confidence to make more changes to how they treat hypos, high blood sugars & use temporary basal rates
- 88% agreed that their anxiety levels had improved since using a CGM
- 98.5% believe that their child's long term management of their T1 diabetes would benefit with full-time CGM

We asked the child/young person why they wanted a CGM; we received various quality of life improvement comments e.g. “I won't have to finger prick all the time”; “So I can feel safer when I'm high or low & it can be caught before it gets bad”; “I would get less worried about diabetes”; “I wouldn't worry about going low and dying when I'm asleep”. There were many more.

Conclusion: This survey showed that the use of CGMs significantly helped with the management of diabetes. The data also suggests that CGM helped young people with diabetes to manage their condition better & more independently in different settings. Based on data, it seems that there is a need for nationally agreed and easy pathway to secure appropriate funding for CGMs.

Oral Session VII - BMI in Type 1 and Type 2 Diabetes

O49

Trajectories of body mass index over adolescence among individuals with type 1 diabetes from a large German/Austrian/Luxembourg Registry: a longitudinal group-based modeling approach

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Objectives: The aim was to identify patterns of age- and gender-adjusted BMI (BMIz) from childhood to young adulthood in subjects with T1D.
Methods: 5,243 subjects (52% boys) from the multicenter diabetes prospective follow-up registry DPV were analyzed (follow-up from age 8-18 years, baseline diabetes duration ≥1 years, BMIz aggregated per year of life). We applied latent class growth modelling (LCGM,SAS:PRO TRAJ) as trajectory approach to identify distinct subgroups following a similar BMIz pattern of change over time.
Results: At baseline (age 8 years), median diabetes duration was 3.4 [Q1; Q3:2.0;5.2] years and BMIz was 0.3 [-0.2;0.8]. Six distinct longitudinal trajectories of BMIz were determined (Fig1). Differences were found for age at onset, sex, migration background, HbA1c, insulin dose, frequency of self-monitoring of blood glucose (SMBG) and of physical activity, height, diagnosis of eating disorders, and dyslipidemia (all p< 0.05), but not in pump use (p = 0.58). Among subjects in the "overweight" group, higher HbA1c, older age at onset, and higher proportion of migration background were observed. In the "low" trajectory, more subjects with eating disorders (girls:5.3%,boys:1.7%), reduced height, but high frequency of SMBG were found. In the "weight-gain" class were less boys (39%), whereas in the "weight-loss" pattern were predominantly boys (67%).
Conclusion: Using the trajectory approach, we determined six distinct longitudinal patterns of BMIz during puberty.

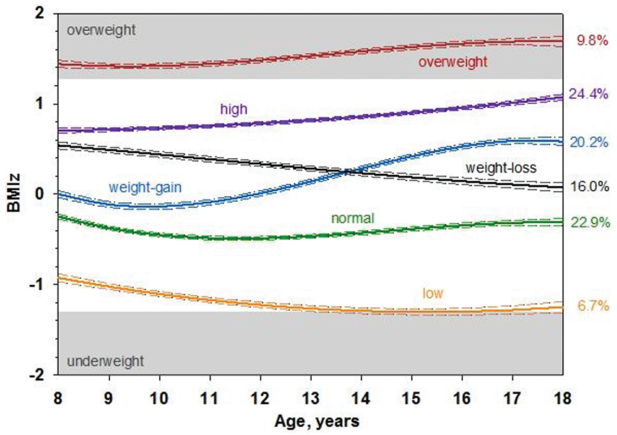

Figure 1. *depicts age- and gender-adjusted BMI (BMIz) trajectories from childhood to young adulthood. BMIz values are based on German national references.*

O50

The relationship between body mass index standard deviation score, glycemic control and insulin therapy in children with type 1 diabetes in the Nordic countries

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Objective: Intensified insulin therapy may increase body mass index standard deviation score (BMISDS). The aim of this study was to investigate the relationships between BMISDS, hemoglobin A_{1c} (HbA_{1c}) and insulin therapy in type 1 diabetes (T1D) children in Denmark, Island, Norway and Sweden.
Methods: Data on gender, age, diabetes duration, HbA_{1c}, insulin dose, severe hypoglycemia, and treatment modality of all children below 15 years of age, with a diabetes duration of more than 3 months, registered in the national childhood diabetes databases during the period 2008-2012 were compiled. We used the Swedish population-based longitudinal values from birth to 18 years of age for height and weight as reference for calculating BMISDS. For the analysis linear mixed longitudinal regression model with repeated measurement design were applied.
Results: There were 11,025 children (52 % females) included in the study. By the last recorded examination of children, median (interquartile range) age was 13.5 years (10.4;14.4), median diabetes duration was 4.3 years (2.2;7.1), median HbA_{1c} was 63 mmol/mol (56.0;71.6), median insulin dose was 0.8 iu/kg/day (0.7;1.0), median BMISDS was 0.70 (0.0;1.4). Median BMISDS was highest in Iceland (0.86) compared to Norway (0.75), Sweden (0.69) and Denmark (0.65). Adjusted mean BMISDS was inversely related to HbA_{1c} across the categories ≤ 58, 58.1-≤ 69 and >69 mmol/mol (P< 0.0001 for all comparisons). Adjusted mean BMISDS increased with insulin dose across the categories ≤0.60 IU/kg/day, 0.61-0.80 IU/kg/day, 0.81-1.00 IU/kg/day and >1.00 IU/kg/day (lowest dose as reference) (P = 0.11, P = 0.048, P = 0.006). Insulin pump users had higher BMISDS compared with pen users (P< 0.0001).
Conclusions: Children with low HbA_{1c}, high insulin dose, and treated with insulin pump have the highest BMISDS. Focus should be on optimizing glycemic control without increasing BMISDS.

O51

BMI-SDS increased only in girls over a 15-year period despite improved HbA_1C for both sexes - data from the Swedish Pediatric Diabetes Quality Register SWEDIABKIDS

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Objectives: Intensified insulin therapy may lead to weight gain and increased body mass index standard deviation score (BMI-SDS) in patients with T1D. The quality of diabetes care in Sweden has improved for the patients aged < 18 years, particularly after 2010. We investigated time trend of BMI-SDS with respect to HbA_1C, gender, current age and age at diagnosis.
Methods: All patients aged < 18 years with T1D registered in the Swedish Pediatric Diabetes Quality Register SWEDIABKIDS during 2000-2014 were included. The Swedish population-based growth reference was used for calculating BMI-SDS. Mean annual BMI-SDS and HbA_1C was calculated for every patient excluding 90 days after the diagnosis. Comparisons were made by 5-year period, sex, age group 0-4, 5-9, 10-14 and 15-17 years, age at diagnosis 0-9 and >9 years and HbA_1C < 52; 52-57; 58-69 and >69 mmol/mol (NGSP < 6.9; 6.9-7.4; 7.5-8.5 and >8.5%). Linear regression was used for the multivariate analyses. Data analysis was stratified by sex due to interaction between sex and the key variables.
Results: Data were available for 14605 patients (6727 girls). Mean HbA_1C decreased by 5-year period: 65.6; 63.6 and 60.6 (p< 0.001). For the girls mean BMI-SDS increased over time 0.68; 0.70; 0.73 (p< 0.001), with increasing HbA_1C (p< 0.001) and increasing age (p< 0.001), especially for the girls diagnosed before 10 years age (p< 0.001). For the boys mean BMI-SDS did not change over time 0.57; 0.52; 0.54 (p = 0.91), it increased with increasing HbA_1C (p< 0.001) and decreased with increasing age (p< 0.001), with no change by age at diagnosis (p = 0.56).
Conclusions: BMI-SDS increased over time in girls but not in boys with T1D in Sweden, although HbA_1C clearly decreased for both sexes. The BMI-SDS increased in girls with less well controlled diabetes and during the puberty. Better diabetes control (lower HbA_1C) was associated with lower BMI-SDS. It is important to prevent weight gain in girls during and after the puberty.

O52
Interstitial glucose and lactate levels are inversely correlated with the body mass index: need for in vivo calibration of glucose sensor results with blood values in obese patients

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Method: Combining microdialysis with a bioanalytical microsystem, the interstitial glucose and lactate concentrations of eight male volunteers with different body mass index (BMI) were monitored during a two- fold glucose tolerance test over the period of three hours.
Results: Significant correlations were found between abdominally measured sensor results and reference measurements (R^2 = 0.967 for glucose and R^2 = 0.936 for lactate; p < 0.05). The average physiological delay of glucose appearance in the ISF of 4 lean volunteers was 10.1± 0.8 minutes, but 17.0 ± 6.4 minutes in 4 obese volunteers. The physiological delay of the abdominally observed glucose appearance in the ISF correlated positively with the BMI (R^2 = 0.787; p < 0.05). The relative in vivo recovery of glucose and lactate was inversely proportional to the BMI of the volunteers (R^2 = 0.540 for glucose, R^2 = 0.609 for lactate; p < 0.05). One subject with a BMI of > 34 kg/m^2 showed fatty tissue at abdominal as well as antebrachial site. At both sites of measurement significantly reduced tissue glucose values compared to blood glucose values (p < 0.001) has been detected.
Conclusion: A very good correlation between abdominally measured sensor results and reference measurements verified the reliability of the BioMEMS. The abdominally measured glucose level in ISF decreased significantly with increasing BMI. Therefore, an in vivo calibration of glucose levels in ISF with blood levels seems to be necessary especially by measuring glucose levels in fatty tissue of markedly obese subjects.

O53
Prevalence of insulin resistance at 10 years of age in a cohort of very low birth weight infants

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Objectives: To study putative parameters affecting insulin resistance in a cohort of very low birth weight (VLBW) infants at 10 years of age.
Methods: Preterm infant born VLBW between in 2004-2005 were enrolled for a follow-up visit at the age of 10 years. During the visit we collected anthropometric parameters as well as glycemia and insulinemia after 8 hours of fasting (calculated HOMA index was considered elevated above 3). We also collected data measured during pediatric follow-up (length, weight and head circumference SDS at birth, at term, at 6, 12, 24 months of corrected age). Patient were defined small for gestational age (SGA) if having a weight < 10^{th} centile and extra-uterine growth restricted (EUGR) if having a difference of weight SDS between term and birth of >-1. For EUGR patients we calculated if and when they recovered the birthweight-SDS and their target height SDS (TE). Catch-up growth was defined both for length and weight as being above the 10^{th} centile.
Results: Of the 30 VLBW infants enrolled, 9 had a HOMA >3. 18 of them were females, while 8 were SGA, and 22 had EUGR. 18 patients recovered their birthweight at 6 months, while 15 and 22 recovered at 12 and 24 months, respectively. Similar values were observed for length (20, 22 and 23, respectively). 14 reached their TH at 24 months, while 20 at 10 years. No risk was found in giving a HOMA >3, except for not catching up weight at 12 months, which seemed protective (RR 0.134, .019-.939). Similarly, no correlation was observed between continuous variables and HOMA, except for a positive trend between weight and length at 12 months (Pearson index .352 and .408, respectively).
Conclusions: Despite only 20 children reached their TH, a high incidence of elevated HOMA at 10 years was found. With the limit of such a small population, being heavier and longer at 12 months of life seems to increase the risk, even if not confirmed at 6 and 24 months.

O54
Insulin sensitivity in obese adolescents versus obese adults with prediabetes: who fares worse?

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Objectives: Youth type 2 diabetes mellitus (T2DM) occurs decades earlier than adult T2DM and is characterized by high therapeutic

failure rates and decreased response to insulin sensitizers suggesting a more severe disease process than in adults. To explain these observations, we investigated if insulin sensitivity (IS) is worse in obese youth than adults with prediabetes at high risk for T2DM.

Methods: Obese youth (age 14.5 ± 0.5 yrs [SE]; 71% Tanner stage V) with impaired glucose tolerance (IGT) were matched 2:1 for BMI, sex and race to obese IGT adults (age 44.7 ± 1.7 yrs). Fasting lipids, fasting hepatic IS ([6,6-$^2H_2$]glucose), peripheral IS (hyperinsulinemic-euglycemic clamp) and body composition (DEXA) were examined.

Results: Despite similar % body fat, HbA1c and 2-hr OGTT glucose, IGT youth had lower hepatic and peripheral IS, higher fasting insulin, and lower HDL compared with IGT adults (Table). However, adults had higher total, LDL and non-HDL cholesterol.

Conclusions: Obese youth with prediabetes are ~50% more insulin resistant, and worse off than obese adults with prediabetes in spite of similar adiposity. This could potentially explain the earlier onset of T2DM in youth and their lower therapeutic response to insulin sensitizers through an early and amplified burden on a β-cell destined to decompensate. However, obese adults with prediabetes manifest worse atherogenic lipid profile than youth highlighting an enhanced risk of CVD in adults.

Variables	Youth (n = 34)	Adults (n = 17)	P
Percent body fat (%)	43.9 ± 0.9	44.8 ± 1.8	NS
HbA1c (%)	5.3 ± 0.1	5.4 ± 0.1	NS
OGTT 2-hr glucose (mg/dL)	154.2 ± 4.5	158.9 ± 4.3	NS
Fasting insulin (μU/mL)	45.0 ± 4.9	20.0 ± 1.5	<0.0001
Hepatic IS (mg/kgFFM/min·μU/mL)-1	8.2 ± 1.2	17.1 ± 1.6	<0.0001
Peripheral IS (mg/kgFFM/min per μU/mL)	4.1 ± 0.4	7.0 ± 0.6	0.002
Total cholesterol (mg/dL)	166.3 ± 6.9	201.4 ± 9.7	0.009
HDL (mg/dL)	38.5 ± 1.0	49.9 ± 4.7	0.035
LDL (mg/dL)	100.3 ± 6.2	129.6 ± 8.1	0.007

[Characteristics of youth vs. adults with IGT.]

O55
Predictors of response to add-on insulin therapy in youth with type 2 diabetes (T2D) in the TODAY trial

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Objective: To understand factors associated with glycemic control after starting insulin in recent-onset T2D youth in the TODAY study following glycemic failure (persistent A1c ≥8%) with metformin +/- rosiglitazone.

Methods: Change in A1c after add-on insulin therapy and the factors predictive of glycemic response were evaluated. At 1 year post-insulin initiation, 253 obese individuals had at least 2 A1c values and mean of 3.9±1.0 visits. Participants were divided into 3 groups according to glycemic control: consistent decrease in A1c by ≥ 0.5%, no change, or consistent increase in A1c ≥ 0.5%, at 75% or more of the visits.

Results: At randomization (baseline) and at time of insulin addition, the 3 groups were similar in age, sex, race-ethnicity, pubertal stage, BMI z-score, T2D duration, and oral glucose tolerance test (OGTT) derived insulin secretion indices (Table). Consistent A1c improvement associated with higher insulin sensitivity (1/fasting insulin) at randomization and at time of failure, higher total and high molecular weight (HMW) adiponectin at randomization and higher A1c at failure.

	"Consistent" A1c Reduction of ≥0.5% (A, n = 84)	No change/ Up and Down A1c ±0.5% (B, n = 117)	"Consistent" A1c Increase of ≥0.5% (C, n = 52)	P-value
At randomization NHB/H/NHW (%)	41.5/40.2/18.3	42.5/37.7/19.8	43.7/43.7/12.5	ns
Age (yr)	13.5 ± 2.0	14.3 ± 2.0	14.0 ± 2.1	0.054
A1c (%)	6.3 ± 0.7	6.5 ± 0.8	6.4 ± 0.7	ns
Total adiponectin (ng/mL)	5979 ± 2541	5198 ± 2239	5293 ± 2211	0.040 A vs B (adj. for race/ ethnicity)
HMW-adiponectin (ng/mL)	3202 ± 1849	2770 ± 1744	2738 ± 1710	0.046 A vs B,C (adj. for race/ ethnicity)
1/Fasting insulin (mL/uU)	0.052 ± 0.036	0.043 ± 0.036	0.047 ± 0.041	0.020 A vs B
C-peptide Disposition Index (ΔC-peptide/Δ glucose at 30 minutes of the OGTT x 1/fasting insulin)	0.0025 ± 0.0025	0.0020 ± 0.0021	0.0023 ± 0.0031	ns
At time of insulin initiation (2.6 yrs post-randomization) A1c (%)	11.1 ± 2.0	9.8 ± 1.7	9.1 ± 1.4	0.0001 ALL
1/Fasting insulin (mL/uU)	0.060 ± 0.043	0.042 ± 0.035	0.045 ± 0.032	0.001 A vs B,C (adj. for A1c at time of failure)

[Characteristics of the 3 glycemic response groups.]

Conclusions: Response to add-on insulin therapy was highly variable. Greater insulin sensitivity and higher adiponectin levels at baseline were associated with improved glycemic control after addition of insulin. It remains to be determined to what extent psychosocial variables and adherence to the prescribed insulin regimen play a role. This needs to be addressed in future studies.

O56
Insulin resistance, impaired fasting, glucose intolerance and type II diabetes mellitus in overweight and obese children in Abu Dhabi

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Background: Obesity is increasingly seen in children and youth. It is linked to major health concerns including glucose intolerance and type II diabetes. Childhood obesity in the Gulf and some other regions around the world has dramatically increased to reach an epidemic proportion. We aim to study the prevalence of obesity comorbidities in terms of glucose metabolism in overweight and obese children and adolescents in Abu Dhabi, UAE.

Methods: Overweight and obese children and adolescents are enrolled in an observational, cross-sectional study. Patients had detailed demographic and family history taken. Standardized weight, height, BMI and waist circumference were recorded. Laboratory tests included fasting glucose, insulin and HbA1c were done. Patients who had high fasting glucose or HbA1c had standard oral glucose tolerance test. Insulin sensitivity was assessed by applying HOMA-index.

Results: 216 patients (121 males) were enrolled. Mean age was 10.58 $\pm$ 2.9 years. 93% were obese and 7% overweight. 173 patients had a waist circumference ≥ 90th centile. 147 patients (74.2%) were insulin resistant. 7 patients were diagnosed with diabetes (6 had HbA1c above 6.5, 1 had 2 fasting glucose measurements above 7 mmol/L). 87 (43.5%) had an indication for OGTT; 26 elevated fasting, 50 elevated HbA1c, 11 had both. 15 patients (8.2%) had impaired glucose tolerance and 37 (18.1) had impaired fasting. 5 patients of 11 with impaired fasting (45.5%) and 8 patients of 50 elevated HbA1c (17.4%) had glucose intolerance.

Conclusions: Insulin resistance is common in overweight and obese children and is more commonly seen in older children with high weight, height and waist circumference. Higher yield of glucose intolerance is obtained when screening utilized combination of high fasting glucose and HbA1c.

Oral Session VIII - Immunology/Various

O57

Increased neutrophil infiltration in pancreas of live resent onset type 1 diabetes patients from the DiViD study compared to pre-diabetic and non-diabetic organ donors from nPOD

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Objectives: Increasing attention is being directed toward the role of innate immune cells as contributing factors to the pathogenesis of type 1 diabetes (T1D). The number of circulating neutrophils has been shown to be decreased in autoantibody-positive (AAb+) individuals and new-onset T1D patients. Accumulation of neutrophils has been described in pancreatic exocrine tissue of a few cases with T1D, suggesting a sequestration of neutrophils in the pancreatic tissue. The aim of the present study was to identify the presence of neutrophils in pancreata of resent onset T1D patients (DiViD), and in different cohorts of organ donors (nPOD).
Methods: Pancreatic specimens obtained from 5 recent-onset T1D patients included (DiViD) and from nPOD donors (4 long-standing T1D, 4 AAb+ and 6 non-diabetic controls) were investigated. Immunohistochemical staining was performed on formalin-fixed, paraffin embedded sections to study the expression of myeloperoxidase (MPO), a marker for neutrophils. MPO+ cells were quantified in the whole area of each section. The ratio between MPO+ cells and each pancreatic section's area was calculated and data were expressed as MPO+ cells/mm2. Differences between groups were assessed by Mann-Whitney U test and $p < 0,05$ was considered as statistically significant.
Results: T1D patients from the DiViD cohort showed MPO+ cells scattered in pancreatic exocrine tissue but also within several isles. The number of MPO+ cells was comparable to that of T1D donors, and higher compared to AAb+ and CTR donors ($p = 0.0162$ and $p = 0.0007$ respectively).
Conclusions: Detection of neutrophils, mainly within the exocrine tissue, suggests an immune infiltration affecting the whole pancreas and not only pancreatic islets. The identification of neutrophils in pancreatic tissue of T1D at disease onset supports the hypothesis that the innate immune system has of a key role of in T1D. This may indicate the presence of an infectious agent in pancreas at onset of disease.

O58

Gut bacteriome and virome at the onset of type 1 diabetes: a study from four geographically distant African and Asian countries

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Objectives: Microbial taxonomic entities associated with type 1 diabetes (T1D) remain largely unknown. So far performed unbiased metagenomic studies have been limited to populations of Europe (mostly North-Eastern), USA and Mexico. We therefore set out to characterize the gut virome and bacteriome from African and Asian children shortly after T1D onset, and compare them to matched controls.
Methods: Samples from 73 children and adolescents were collected shortly after T1D onset (Azerbaijan 19, Jordan 20, Nigeria 14, Sudan 20 cases), along with 104 control subjects of similar age and place of residence. The virome was characterized by unbiased mass sequencing of virus-enriched stool fraction and by specific PCR tests, whereas the bacteriome was profiled by mass sequencing of 16S ribosomal DNA amplicons. Methods of multilevel modeling were used to assess the association, adjusting for the different geographic origin of samples.
Results: A significant positive association with T1D was noted for the genera of *Escherichia* (class *Gammaproteobacteria*, phylum *Proteobacteria*), *Prevotellamassilia* (c. *Bacteroidia*, p. *Bacteroidetes*) and *Megasphaera* (c. *Clostridia*, p. *Firmicutes*). Significant negative associations were observed for several genera of the class *Clostridia* (p. *Firmicutes*), with the strongest effect of *Pseudobutyrivibrio*, *Eubacterium* and *Roseburia*. Several further association signals were limited to a single population only. No clear association signals were noted among the human viruses. The risk effect of the HLA-DQ2 and/or DQ8 molecules was strongly expressed, whereas the protection by HLA-DQB1*0602 was attenuated.
Conclusions: It appears that some degree of distortion in the gut bacteriome upon T1D onset is a global feature. It remains to be established whether the observed associations are due to the ability of the certain taxa to accelerate islet autoimmunity, or whether, contrarily, the early diabetic state causes a microbiome change.

O59

CIS promotor polymorphism effects on T-cell cytokine receptor signaling and type 1 diabetes susceptibility

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Objectives: This is the first report about a possible role of CIS (Cytokine-Inducible SH2 containing protein, encoded by *Cish*) genetic variants in Type 1 Diabetes (T1D). The important influence of CIS on the regulation of IL-2 receptor signaling is well established and previous studies identified association of functional CIS variants with susceptibility to infectious diseases (i.e. tuberculosis, malaria). Because of the central role of IL-2 receptor signaling in T1D, we determined CIS variant frequencies in T1D patients and characterized functional effects on T-cell cytokine receptor signaling.
Methods: 262 patients with T1D (>10 years after clinical onset, onset age < 5 years) recruited for the pediatric diabetes biobank within the German Center for Diabetes Research (DZD) were genotyped for *Cish* SNPs (i.e. rs809451/rs414171). Minor Allele Frequencies (MAFs) were compared with the caucasian cohort from the 1000

genome project. For characterization of T cell functions, CIS-mRNA and STAT5 phosphorylation were quantified in PBMC of *Cish* SNPs genotyped healthy donors stimulated with IL-2 and IL-7.
Results: T1D patients MAFs for rs809451 (11.5%) and rs414171 (12.2%) were comparable to the European cohort of the 1000 genomes database. Functional T-cell analyses detected IL-2- and IL-7 induced CIS mRNA expression and STAT5 phosphorylation but no significant differences for heterozygous minor allele carriers. Differential CIS mRNA induction in a homozygous minor allele carrier did not affect IL-2 or IL-7 receptor signaling regulation.
Conclusions: Our results do not suggest a role of described CIS polymorphisms in T1D T-cell responses. However, our study demonstrates the necessity of functional T-cell analyses to evaluate the relevance of disease-associated genetic variants.

O60
Can mice reproduce the human gut bacteriome? A lesson from two children representing the extremes of beta cell loss within an intervention trial with gluten-free diet

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Background: Presently, the period shortly after type 1 diabetes onset is a setting most often used for testing of interventions possibly slowing the progression of insulitis. Our group is currently running a study with gluten-free diet. Here we present results of two human microbiota transfers to colonies of germ-free NOD mice: each from a child at one extreme of the main outcome, the C-peptide response.
Methods: Twenty four children have been recruited shortly after type 1 diabetes onset and followed up in a protocol that includes three mixed-meal tolerance tests and regular collection of stool samples. Thirteen of these children were assigned to the intervention with gluten-free diet. Fresh stool samples were immediately processed and frozen for a later transfer to germ-free NOD mice colonies that were then kept on a standard sterile gluten containing chow. Mice fecal bacteriome profiles were then individually assessed in regular intervals.
Results: Patients did not differ in gut bacteriome diversity by their intervention assignment and their bacteriomes were mostly resilient. The adopted mice microbiome profiles were of significantly lower diversity ($p < 10^{-5}$) than the donor material, mostly due to the enrichment of *Bacteroidetes* to the detriment of depleted *Firmicutes* genera. This may reflect different sensitivity of anaerobes to oxygen during processing, or a different ability of humans versus mice to host individual species. Interestingly, many important species adequately reflected the human abundance, e.g. *Akkermansia*. The profiles were tightly linked across the mice colony, and evolved only slightly over the observation period.
Conclusions: Germ-free NOD mice administered with human gut microbiome are able to adopt a large part of the bacterial content, although the ratios of main phyla are reproduced suboptimally. The use of this model may help dissect the influence of the gut bacteriome from the net effect of gluten-free diet.

O61
Identification of a novel *KLF11* mutation in siblings with autoantibody-negative type 1 diabetes

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Objectives: *KLF11* encodes a transcriptional factor that regulates mRNA expression of the insulin gene. To date, two *KLF11* mutations with ~50% of residual activity (p.T220M and p.A347S) have been identified in three families (eight patients) with early-onset type 2 diabetes. In this study, we identified a hitherto unreported *KLF11* mutation in two siblings clinically diagnosed with type 1 diabetes.
Methods: Our subjects were a 14-year-old boy and his 9-year-old sister who developed type 1 diabetes at 1.5 and 1.1 years of age, respectively. They had no diabetes-associated autoantibodies at the diagnosis. Both siblings required insulin therapy. Their mother was diagnosed with autoantibody-negative type 1 diabetes at age 3 years, and treated with insulin. To clarify the etiology of diabetes, we performed whole exome sequencing of the siblings.
Results: A heterozygous missense variant in *KLF11* (c.1203C>G, p. H401Q) was identified in both siblings. This variant has not been reported previously, and was not registered in polymorphism databases (ExAC, 1000 Genomes, HGVD and HGMD). 3D structure simulation analysis suggested that the p.H401Q mutation affects a functionally important histidine residue in the zinc finger domain of KLF11.
Conclusions: This is the first report of the identification of a *KLF11* mutation in patients with type 1 diabetes. The phenotypic difference between our patients and previously reported cases may reflect the difference in the residual activities of the mutant proteins; it is possible that the p.H401Q mutation leads to a more severe functional defect than the hypomorphic p.T220M and p.A347S mutations. Our findings expand the phenotypic spectrum of *KLF11* mutations.

O62
Next generation sequencing for the diagnosis of rare forms of monogenic diabetes: a new clinical-molecular approach for accurate diagnosis

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The underestimation of the prevalence of monogenic diabetes is often due to misdiagnosis related to the wide range of etiologies and

variable clinical features. Maturity Onset Diabetes of the Young (MODY) represents the most common type of monogenic diabetes. Unfortunately, some subjects do not find an etiologic diagnosis and they are labeled as MODY X or misdiagnosed as type 1 (T1D) or 2 (T2D) diabetes. A proper diagnosis is pivotal for screening program, familial counselling and, above all, tailoring the best treatment.
Objectives: To use the fast and economical method of Next Generation Sequencing (NGS) to study subjects with MODY X and cases labeled as T1D or T2D, which however had atypical characteristics (absent/low-autoimmunity, low insulin requirements, strong familiarity, no overweight).
Patients and Methods: 79 cases of confirmed hyperglycemia referred to our Pediatric Diabetes Center from January 2014 to December 2016 were analyzed and 10 MODY X and 6 atypical T1D or T2D underwent to a specific panel of 15 genes known to be associated with genetic forms of diabetes with the NGS.
Results: 7 gene mutations were found in 6 patients (3 MODY X and 3 T1D cases): 1 case of mutation in exon 2 of the Wolframin gene, determining a stop codon (not previously described); 1 case of mutation on a splicing site in the insulin gene (novel mutation) (MODY 10); 1 case of missense mutation in the KCNJ11 gene already known as pathogenic (MODY 13); 1 case of missense mutation in the BLK gene, of probable pathogenic nature (MODY 11); 1 case of compound heterozygous missense mutations in the KLF11 gene (known as pathogenic) and in the CEL gene (known as pathogenic) (MODY 7 and 8); 1 case of missense mutation in the GCK gene, known as pathogenic (MODY 2).
Conclusions: The development of new NGS-based genetic tests can allow a cost-effective and rapid molecular diagnosis of many forms of diabetes, enabling the detection of mutations in rare genes related to monogenic diabetes.

O63
A cell cycle regulator as a potential therapeutic target for Wolfram syndrome

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Introduction: Wolfram syndrome is a monogenic form of diabetes mellitus and neurodegeneration, but the mechanism for neuron and pancreatic beta cell death is unclear. We showed that significant $p21^{cip1}$ downregulation was present in WFS1-depleted cell lines; however, when present, the expression of $p21^{cip1}$ was associated with the inhibition of progression through the G2 phase of the cell cycle, and prevention of neuronal apoptosis. Here, we tested the hypothesis that upregulation of $p21^{cip1}$ expression will prevent neuronal apoptosis in Wolfram syndrome.
Methods: We performed a drug screen using High Content Cytometry, selecting drugs known to increase $p21^{cip1}$ expression. We then treated cells with 0.1-10micromolar valproic acid for 72 hours, and determined the effects on $p21^{cip1}$ expression and apoptosis. Finally we analysed data from microarray of genes affected by sodium valproate in lymphocytes (GSE65297).
Results: Of 26 drugs screened, 5 showed evidence of increased $p21^{cip1}$ expression. We selected valproic acid to take forward due to its known safety profile and ability to cross the blood-brain barrier. In all concentrations tested (0.1-10 microM), valproic acid treatment significantly increased expression of $p21^{cip1}$ by 20-30% in KD cells compared to controls; and reduced the expression of cleaved-caspase3 by up to 40% in KD3 cells. On microarray analysis, valproic acid downregulated genes involved in ER stress and apoptosis, and induced the gene for $p21^{cip1}$.
Summary and Conclusions: We implicate $p21^{cip1}$ as a mechanism for prolonging cell survival in Wolfram syndrome. The expression of $p21^{cip1}$ is reduced in WFS1 depleted neuroblastoma cells and reduced expression of $p21^{cip1}$ correlates with cell death. Valproic acid, a commonly used mood stabilizer has been reported to upregulate $p21^{cip1}$ expression in various cell models. Our results suggest the potential therapeutic effects of valproic acid in the treatment of neurodegeneration in Wolfram syndrome.