ISPAD 2023 – JP's reporting!

ISPAD 2023 was an outstanding conference. Science intersected with the everyday concerns of the diabetes team. Here's a concise summary of the main themes:

T1D isn't solely a beta cell problem but a pancreas dysfunction. After eating, those with T1D see Glucagon spikes that heighten post-prandial hyperglycaemia. Synthetic Amylin and GLP-1 are promising for improving several metrics, including time in range. There's an absence of glucagon during hypoglycaemia in T1D due to paracrine signalling failure. Studies in mice suggest Somatostatin receptor agonists might address this. Future treatments for T1D might combine insulin, GLP-1, Amylin, and somatostatin.

A major focus was on preserving b-cell function in T1D. Several immunomodulators have shown effectiveness in retaining C-peptide up to 24 months post-diagnosis. One even delayed T1D stage 3 by 2.5 years. Anti-retroviral drugs also play a role in C-peptide preservation. However, there's a need for a balanced view on the prolonged use of immunomodulating therapies. While their benefits are evident in rheumatoid arthritis and oncology, they may not be directly comparable. The fear is that the focus might shift only to prevention, leaving those already with T1D without access to Automated Insulin Delivery (AID).

AID systems are transformative. They're not only effective but also cost-efficient. Starting AID early can mitigate the detrimental effects of initial high glucose exposure. It's crucial to reduce racial and social disparities in glucose control.

Practical management tips for AID were shared. For exercise, the 25-25 target is recommended, and a 10-minute activity can reduce glucose by 2 mmol/L. Before drinking alcohol, ensure exercise targets are met. If carbohydrate counting is challenging, personalised set amounts can help. For young children, fostering healthy eating habits is vital. Strategies include family meals, a nutritious food environment, and maximising pump benefits. Food times should remain calm with repeated offers of healthy choices.

To foster a culture of continual improvement in teams, ensure a shared vision. Everyone should have development opportunities and clear responsibilities. Embrace failures, as they provide learning experiences. Lastly, for written communication, adopt brief, clear sentences and voice a single idea per sentence. Always review before sending.

Read the next pages for a deeper review.

ISPAD Day 1

Glucagon Secretion Control and Implications for Type 1 Diabetes Management

Introduction:

ISPAD day 1 provided valuable insights into the intricate regulation of glucagon secretion and its relevance in the context of type 1 diabetes (T1D). This report summarises key findings presented during the conference and explores potential therapeutic approaches to address glucagon dysregulation in individuals with T1D.

Glucagon Secretion and Hypoglycaemia:

One central question posed during the conference was whether the control of glucagon secretion is dependent on the interplay between islet cells. Existing data strongly suggest that in individuals with T1D, the loss of glucagon secretion following hypoglycaemia appears to be irreversible. However, it is worth noting that this impairment seems to be specific to hypoglycaemia, as various other stimuli, such as intravenous and oral amino acid administration, insulin withdrawal, lipopolysaccharide exposure, and exercise, elicit significant glucagon responses, albeit attenuated when compared to nondiabetic individuals.

Glucagon Hypersecretion:

Beyond hypoglycaemia, individuals with T1D display glucagon hypersecretion after meal tests, potentially contributing to hyperglycaemia and insulin resistance. The complexity of these phenomena may be attributed to the activation of distinct regulatory pathways governing glucagon secretion, including intra-islet paracrine signalling, direct signalling, and autonomic signalling. As such, further investigations into this conundrum are warranted.

Residual C-peptide and Glucagon Regulation:

One notable observation discussed at the conference was that individuals with T1D who possess residual C-peptide production tend to experience a more favourable glucagon response. This suggests that these individuals maintain some of the complex signalling pathways required for the regulation of glucagon secretion.

Potential Therapeutic Approaches:

The conference also explored potential therapeutic avenues to address glucagon dysregulation in T1D. Notably, in isolated human islet cells, the use of somatostatin receptor antagonists has shown promise in halting somatostatin release and facilitating glucagon

release in response to hypoglycaemia. This represents a promising avenue for future research and treatment development.

Promising Therapies:

Several promising therapies were discussed during the conference:

Pramlintide with Automated Insulin Delivery (AID):

This study demonstrated that the combination of pramlintide with AID systems can achieve target glucose levels (TIR) ranging from 74% to 84%, vs AID alone. [Reference: https://diabetesjournals.org/care/article/43/3/597/35620/A-Novel-Dual-Hormone-Insulin-and-Pramlintide

GLP-1 with Insulin in T1D

Research indicates that combining GLP-1 with insulin in the treatment of T1D can lead to improvements in HbA1c, BMI, and total daily insulin dose (TDD). [Reference: https://pubmed.ncbi.nlm.nih.gov/34463425/

Future Directions:

The conference highlighted ongoing research into the use of GIP (Glucose-Dependent Insulinotropic Polypeptide), GLP-1 (Glucagon-Like Peptide-1), and glucagon receptor modifiers to further understand and potentially modulate glucagon secretion in individuals with T1D. These endeavours hold promise for the development of innovative therapies to improve the management of T1D.

Conclusion:

This data provides valuable insights into the regulation of glucagon secretion and its implications for individuals with T1D. While challenges remain, the research presented underscores the importance of further investigations and the potential for innovative therapeutic approaches to address glucagon dysregulation in T1D. Future studies and clinical trials hold the key to advancing our understanding and improving the management of this complex condition.

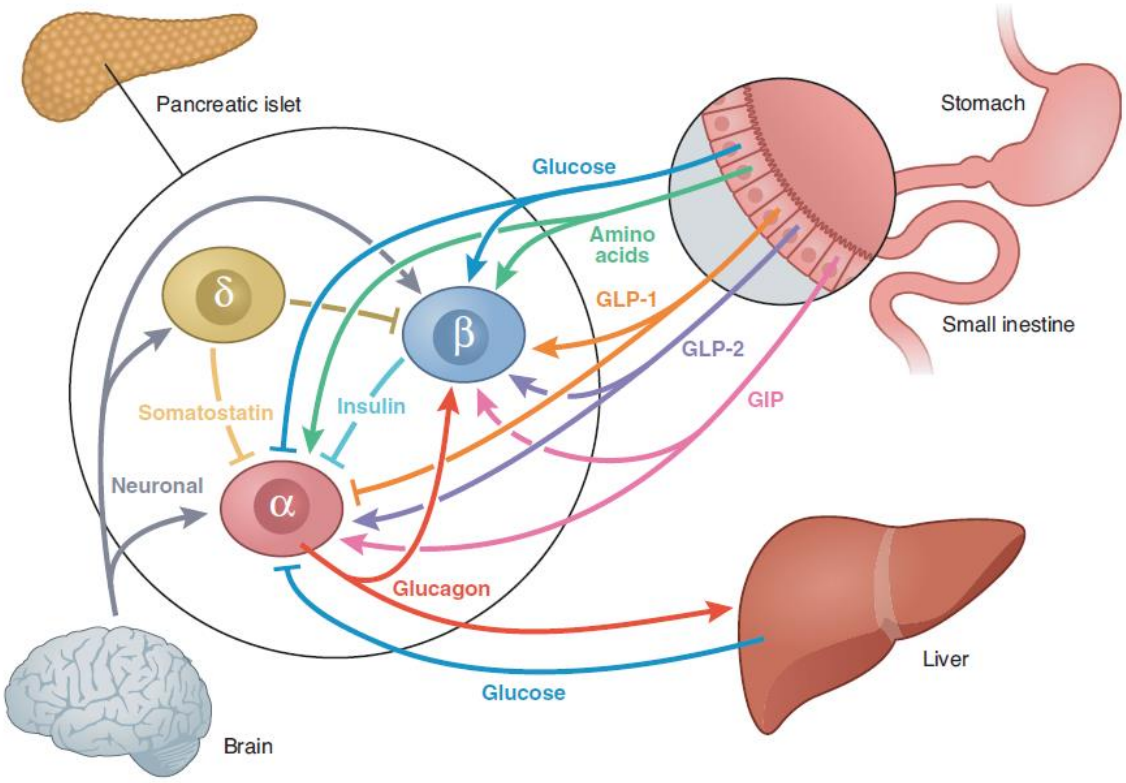


FIGURE 1 The alpha cell glucagon regulation. Alpha cell glucagon secretion is regulated by nutrients (amino acids), indirectly (and perhaps directly) by glucose, the autonomic nervous system (neuronal innervation from the brain), gut incretins and direct/indirect paracrine signaling from beta cells and delta cells within the pancreatic Islets of Langerhans. α = alpha cell. B = beta cell. Δ = delta cell. GLP-1, Glucagon-like peptide 1; GLP-2, Glucagonotropic glucagon-like peptide 2; GIP, Glucose-dependent insulinotropic polypeptide

John's thoughts:

1. We're shifting from using Glucagon as a dual hormone to utilising synthetic Amylin and GLP-1 because they offer improved control over post-meal glucagon levels and enhance Time in Range (TIR).

2. A once-a-week injection of GLP-1 might not just enhance TIR but also help manage weight in children and young people with a BMI above the 91st percentile.

3. At what age would it be considered safe? It appears that 12 years and older, based on data from type 2 diabetes and obesity cases. However, we need to carefully weigh the long-term risks versus the benefits of using dual agents.

Nutrition and AID

Study Title: Simplified Meal Announcement Versus Precise Carbohydrate Counting in Adolescents With Type 1 Diabetes Using the MiniMed 780G Advanced Hybrid Closed Loop System: A Randomized Controlled Trial Comparing Glucose Control

Introduction:

On Day 2 of the ISPAD conference, a study was presented that investigated the impact of different meal announcement approaches on glucose control in adolescents with type 1 diabetes (T1D) utilizing the MiniMed 780G Advanced Hybrid Closed Loop System. The study aimed to compare glucose control between adolescents who used simplified meal announcements and those who practiced precise carbohydrate counting.

Methods:

This randomized controlled trial enrolled 34 participants aged 12 to 18 years with T1D, who were either on multiple daily injections or insulin pumps. These participants were preparing to initiate the use of the MiniMed 780G system at Sidra Medicine in Qatar. Following a 7-day run-in period, the participants were randomly assigned to one of two groups: the "fix" group, which utilized simplified meal announcements with pre-set personalized fixed carbohydrate amounts, or the "flex" group, which practiced precise carbohydrate counting. The study spanned 12 weeks, with the primary endpoint being the difference in time spent in the target glucose range (Time in Range or TIR) between the two groups. Secondary endpoints included HbA1c and other glucose metrics measures.

Results:

Over the 12-week study period, the flex group achieved a TIR of 80.3 ± 7.4%, while the fix group reached a TIR of 73.5 ± 6.7%. This resulted in a statistically significant difference of 6.8% in favour of the flex group ($P = 0.043$). The flex group also demonstrated better control of glucose levels above 250 mg/dL ($P = 0.012$), while no significant differences were observed in HbA1c ($P = 0.168$), time below the target glucose range ($P = 0.283$), and time spent between 180 and 250 mg/dL ($P = 0.114$).

Conclusions:

Adolescents using the MiniMed 780G system with pre-set personalised fixed carbohydrate amounts can achieve internationally recommended targets for glycaemic control. This suggests that simplified meal announcement may serve as a valuable alternative to precise carbohydrate counting for users who find precise counting challenging. Nevertheless, it is

important to note that precise carbohydrate counting still offers benefits, and its skills remain relevant for MiniMed 780G users.

John’s thoughts:

1. Here's the suggested approach: (a) Start with carb counting as the primary method. (b) If you encounter difficulties with carb counting, whether it's due to math or practical challenges, consider seeking a dietetic assessment. This assessment can provide prescribed carb values for meals based on your typical intake.

2. We should conduct an audit of this approach to assess whether it leads to improvements in glycaemic control, the frequency of boluses per day, and other relevant factors. Let's call this initiative "Anjanne's Project!"

BMI Stability with Advanced Hybrid Closed Loop Systems: Another study discussed during the conference investigated the influence of advanced hybrid closed loop systems on the body mass index (BMI) of children and adolescents with T1D. The study found that after 1 year of using the Medtronic MiniMed 780G Advanced Hybrid Closed Loop system, there was no significant change in BMI. While there was a slight increase in total daily insulin per kg of body weight, the percentage of basal insulin remained stable. Furthermore, glycaemic control parameters remained consistent over the study period.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9592809/

John's thoughts:

1. Our audit should focus on changes in BMI Z-scores at the one-year mark. Specifically, we should examine three groups: those with BMI below the 9th percentile, those between the 9th and 91st percentiles, and those above the 91st percentile. This analysis will help us understand the outcomes in each group.

Future Innovations in Diabetes Technology: The conference also featured discussions on future innovations, including the integration of Libre 2 technology into diabetes management. The RADIANT RCT Trial involving 200 paediatric and adult patients was highlighted. However, it was noted that a lack of calibrations in sensor technology may pose challenges in terms of sensor turnover and patient and family confidence.

John's thoughts:

1. What happens if the patient's Self-Monitoring of Blood Glucose (SMBG) reading differs by more than 20% from the expected value? Do they need to replace the sensor? Does it affect the system's confidence? Will they exit the open-loop mode until the sensor returns to accurate readings?

ISPAD 2022 exercise guideline recommendations into practical heuristics. Skin in the game = those giving advice must remember that guidelines are intended to offer guidance, not to be treated as law. The process of implementing guidelines is akin to transforming scientific knowledge into an art form, Birmingham Style Diabetes Art. For instance, creating art such as 10 minutes of moderate-intensity activity between meals can reduce glucose levels by approximately 2.0 mmol/L (source: https://www.hindawi.com/journals/pedi/2023/2519368/).

Simplifying the creation of exercise plans for MDI/CSII involves using a 50/50/20 ratio, while AID employs a 25/25/Target approach. These plans must be given along with the fundamental principle that "The Glucose Never Lies," (source: https://onlinelibrary.wiley.com/doi/full/10.1111/pedi.13452).

John's thoughts:

1. What a speaker! (jokes!)

ISPAD Day 2 highlights

The Impact of Early Closed-Loop Therapy on Type 1 Diabetes

The CLOuD study marked a significant milestone in the exploration of long-term treatment effects utilising a closed-loop system, specifically the CamAPS FX, shortly after the diagnosis of type 1 diabetes. The study aimed to investigate whether this intervention could preserve C-peptide secretion, an indicator of residual beta-cell function. A cohort of 101 adolescents aged 10 to 17, diagnosed with type 1 diabetes, were randomized into either a closed-loop or control group within 21 days of diagnosis, with an initial baseline HbA1c of 10.6%. After two years of treatment, notable improvements in glycaemic control were observed in the closed-loop group (Time in Range [TIR] 64%, HbA1c 6.9%) compared to the control group (TIR 49%, HbA1c 8.0%). This improvement occurred despite a substantial percentage of the control group utilising advanced technology (43% used insulin pumps, and 68% employed continuous glucose monitors).

However, the most significant finding from this study was the lack of impact on C-peptide secretion. In both the closed-loop and control groups, C-peptide levels continued to decrease over the two-year period. The total daily insulin dose, often used as a proxy for endogenous insulin secretion, did not show a significant difference between the two groups, with closed-loop users requiring 1.14 U/kg/day and the control group 1.09 U/kg/day.

In summary, the study suggests that a prolonged period of closed-loop therapy immediately following the diagnosis of type 1 diabetes in children and adolescents does not appear to halt the decline in C-peptide secretion. It raises the possibility that even more stringent glycaemic control, such as achieving normoglycemia, may slow down the C-peptide deterioration. However, it is likely that other factors, such as the strength of the immune response, contribute to the decline of beta-cell function.

While the results may not provide the desired outcome, they offer valuable insights into the mechanisms of type 1 diabetes. Moreover, the study reaffirms that initiating a closed-loop system immediately after a type 1 diabetes diagnosis is safe for children and adolescents, and it provides significantly improved glycaemic control compared to conventional insulin therapy without closed-loop technology. This is of paramount importance when considering the legacy impact of early glucose control.

John's thoughts:

1. AID from diagnosis makes sense as the AID can better adapt to the honeymoon than once a week HCP changes in insulin.
2. The legacy effect of improved glucose control are important.
3. Their will be no extra preservation of residual insulin capacity despite the improved diabetes control.

The Beta-Bionics system

The Beta-Bionics system, which requires only weight input and mealtime information (e.g., breakfast, lunch, or dinner – also are meals usual, small, or big) while relying on artificial intelligence for the rest, represents another promising avenue in diabetes management. The referenced study, titled "Multicentre, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes," presents compelling findings regarding the efficacy of this system in improving glycated haemoglobin levels over a 13-week period.
https://pubmed.ncbi.nlm.nih.gov/36170500/

The trial, involving individuals aged 6 to 79 with type 1 diabetes, revealed a significant reduction in glycated haemoglobin (-0.6% and >10% TIR) levels in the bionic pancreas group compared to standard care. Importantly, the percentage of time spent with glucose levels below 3.0 mmol/L did not differ significantly between the two groups, establishing the noninferiority of the bionic pancreas system. It is noteworthy that no episodes of diabetic ketoacidosis occurred in either group.

In conclusion, the study demonstrates that the bionic pancreas system, initialised primarily based on body weight and requiring minimal user input, offers a promising alternative for managing type 1 diabetes, resulting in improved glycemic control without an increased risk of diabetic ketoacidosis. May be useful for people who want the minimum input?

John's thoughts:

1. Beta Bionics offers simplicity by relying solely on weight, but it achieves a Time in Range (TIR) of 65%, which we can surpass for most individuals through carb counting and streamlined meal management. On the other hand, it might be a straightforward option for those who find nutrition challenging, making it a viable choice in such cases.

Title: "Meet the Editor: Writing and Publishing in High-Impact Journals"

Abstract: Craft a clear and engaging abstract that attracts potential reviewers.

Introduction: Create a compelling narrative to introduce your work.

Methods: Ensure absolute clarity and reproducibility in your methodology.

Results: Present your results objectively and avoid overhyping non-significant findings.

Discussion: Contextualise your work for a broad audience, addressing advancements, challenges, and prior research. Distinguish between statistical and clinical significance, highlight limitations, and specify future research needs and implications.

Cover Letter: Avoid rehashing the abstract; instead, emphasize translational value and potential impacts on clinical practice and patient outcomes.

Top Tips: Read your work aloud to assess flow and consider using shorter sentences. Seek feedback from individuals outside your field to ensure clarity.

Reviewers' Expectations: Reviewers seek novelty, methodological rigor, and unbiased reporting that identifies limitations.

Responding to Reviewers: Address each reviewer's points clearly and confidently, backing up your responses when necessary.

John's recommendations for improving writing:

1. Use shorter, direct sentences, each conveying a single idea. Avoid lengthy, complex sentences that are hard to follow.
2. Read your work aloud to evaluate its flow and coherence.
3. Read it slowly to a family member to check if they can easily understand it.

Disease-Modifying Therapy for Type 1 Diabetes Pathogenesis

T1D caused by insufficient regulation of the immune system can lead to an autoimmune response triggered by autoreactive T cells. This process involves four distinct stages:

Triggers: Various factors, such as nutritional elements, genetic predisposition (approximately 50%), and microbiota imbalances.

Stage 1: At this point, individuals have two auto-antibodies present, but their glucose regulation remains normal.

Stage 2: Individuals in this stage also have two auto-antibodies, but their glucose regulation is now abnormal.

Stage 3: Type 1 diabetes is diagnosed, but there is still some remaining c-peptide production.

Stage 4: B-cell function continues to decline.

Our goal is to diagnose the condition in stages 1 and 2, then gradually introduce disease-modifying therapies (such as immune modulators) and potentially behavioural interventions like exercise.

There are five autoantibodies involved in this process: IAA (Insulin Autoantibodies), IA-2 (Insulinoma-associated Antigen-2), GAD (Glutamic Acid Decarboxylase), ZNT8, and another.

A new biomarker, C-peptide, can assess the current stage of the disease and the response to treatment. Preserving C-peptide levels is considered beneficial.

Strategies for C-peptide preservation include:

Investigating primary prevention through microbiome improvement?

Implementing disease-modifying therapies in stages 1 and 2 (exercise may also be beneficial alongside immune modulators).

Slowing disease progression in stage 3 (exercise and immune modulators may play a role here as well).

Screening for type 1 diabetes has varying sensitivity levels depending on when it is performed. Screening at ages 2-3 yields a sensitivity of 35%, while re-screening between ages 5-7 increases sensitivity to 50%. This approach has its advantages and disadvantages:

Pros:

Reduced incidence of diabetic ketoacidosis (DKA).

Smoother disease onset, longer honeymoon period, and improved long-term outcomes.

Ability to recruit patients for clinical trials when therapies become available.

Cons:

May cause anxiety and demand significant time commitment.

Misses patients who seroconvert after screening due to its 50% sensitivity.

Currently, no definitive treatment exists; only lifestyle modifications are recommended (e.g., physical activity, carbohydrate modification, maintaining a normal BMI z score, and considering omega-3 supplementation).

The DiaUnion screening program.

Swedish screening focuses on screening for a triad of conditions: Type 1 Diabetes (IAA, GADA, IA-2A, ZNT8A), Celiac Disease (IgA-tTG, IgG-tGA), and Thyroid Disorders (TPOA, THGA). Results from this program indicate that 9.3% of individuals screened were positive for one of the triad conditions, with only 2.6% of them being diagnosed with one AA for Type 1 Diabetes. Among those with two autoantibodies and dysglycemia, only 0.1% were diagnosed with Type 1 Diabetes. Additionally, a Danish study was conducted to further investigate these aspects. 13.5% positive screen, 4.6% 1 T1D AA – 1.0% had 2AA and 0.3% diagnosed with T1D.

What should be the support for those identified in stage 2?

For individuals identified in stage 2 of Type 1 Diabetes, it's crucial to understand what this staging means and how to provide support effectively. Here are some key considerations:

Understanding Staging: Staging refers to categorising the progression of the disease. In this context, it helps determine the severity and development of Type 1 Diabetes.

Monitoring: CGM may become is essential. Regular check-ups and assessments can track the progression and response to treatment.

Behavioural Changes: Patients in stage 2 may benefit from adopting certain behavioural changes. These could include incorporating regular exercise into their routine, which can help manage blood glucose levels and overall health.

Dietary Changes: Dietary adjustments are often necessary. Working with a registered dietitian or nutritionist can help individuals manage their diet to better control their blood sugar.

Ensuring a Softer Landing: This phrase means making the transition to life with Type 1 Diabetes as smooth as possible. It involves providing the necessary support and resources to help individuals adapt to their new circumstances and manage their condition effectively.

International Guidance: The JDRF will be providing international guidance based on the ISPAD (International Society for Pediatric and Adolescent Diabetes) guidelines. This guidance will be considered "Expert Opinion" and will serve as a reference for healthcare professionals, patients, and policymakers.

Accessing Funding: To ensure that the relevant support can be provided to those in stage 2 and beyond, it's crucial to use this international guidance as a basis for accessing funding. By aligning with established guidelines, organizations and healthcare systems can secure the necessary resources to assist individuals with Type 1 Diabetes effectively.

T1D immunomodulating therapies

In the CLVer study conducted on individuals aged 7-17 who were in stage 3 of diabetes from the time of diagnosis, Verapamil, a calcium channel blocker, was administered. The study measured C-peptide levels after a mixed meal test as the primary endpoint. It's important to note that the study was not designed with sufficient statistical power to detect differences in secondary endpoints, such as changes in HbA1c (glycated haemoglobin) and continuous glucose monitoring (CGM) metrics. However, the results indicated that C-peptide levels

were 30% higher in the Verapamil group compared to the control group, suggesting that Verapamil preserved beta-cell function.

In the T1GER trial, which focused on Tumour Necrosis Factor-alpha (TNF-α), a cytokine, the group receiving TNF-α treatment showed improved C-peptide levels at the one-year mark.

Rituximab, an anti-CD20 treatment that depletes B cells, led to higher C-peptide levels at the one-year mark but did not maintain this effect at the two-year mark, compared to control.

T-cell targeting therapies designed to prevent T-cell activation, such as Abatacept (involving 112 participants aged 6-36), showed increased C-peptide levels at the two-year mark. The T1DAL study, which also depletes T-cells, demonstrated preservation of C-peptide levels at the two-year mark. Additionally, the PROTECT study involving Teplizumab (another T-cell depletion therapy) for individuals aged 8-17, diagnosed within six weeks, showed higher C-peptide levels at week 78 compared to the control group.

It's worth noting that there are numerous therapies available that can help preserve beta cell function. The future of diabetes management is likely to involve combining these therapies, as a single agent may not be sufficient for effective treatment.

John's thoughts:

1. From a physiological perspective, it seems logical to identify and moderate the immune system early on. This concept appears to be a part of our future.

2. Looking ahead, it appears that we may need to administer multiple agents every 2-3 years for a period of 10-20 years to prevent or significantly delay a particular condition. However, this potential reality could be a decade or two away.

3. The argument here is that patients undergoing oncology treatments, those with rheumatoid arthritis, and individuals with psoriasis often use multiple agents with minimal side effects. Consequently, there's a suggestion that we can extrapolate this safety to other cases, such as T1D. However, we need to carefully assess specific scenarios:

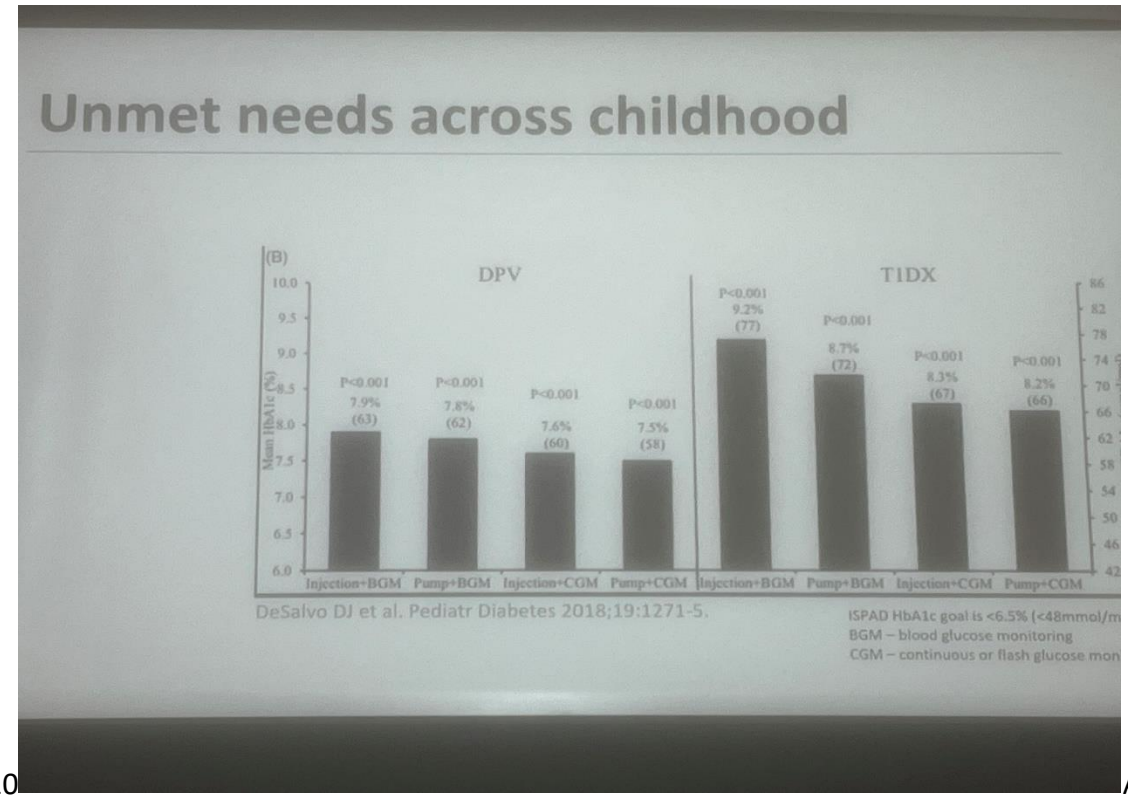
a. In cases like oncology and rheumatoid arthritis, where the conditions are life-threatening and severely debilitating, the threshold for using these treatments should be relatively low. In contrast, type 1 diabetes with autoimmune disorders is not as life-threatening or debilitating, so the criteria for its use should be more stringent.

b. It's important to note that conditions like rheumatoid arthritis and psoriasis typically don't begin treatment at the age of 2 years and aren't administered frequently during childhood development. Therefore, there's limited data available for the scenario of starting early in life, frequent administration, and using multiple immune modulators.

c. While investigating this avenue is undoubtedly worthwhile, we must differentiate the use of these treatments for type 1 diabetes from their use in oncology, rheumatoid arthritis, and psoriasis. We need to balance our excitement for this new approach with the realities of interfering with the biological processes during growth and maturation.

CamAPS FX session – Practical Insights – with YpsoPump

Julia Ware – jf674@cam.ac.uk



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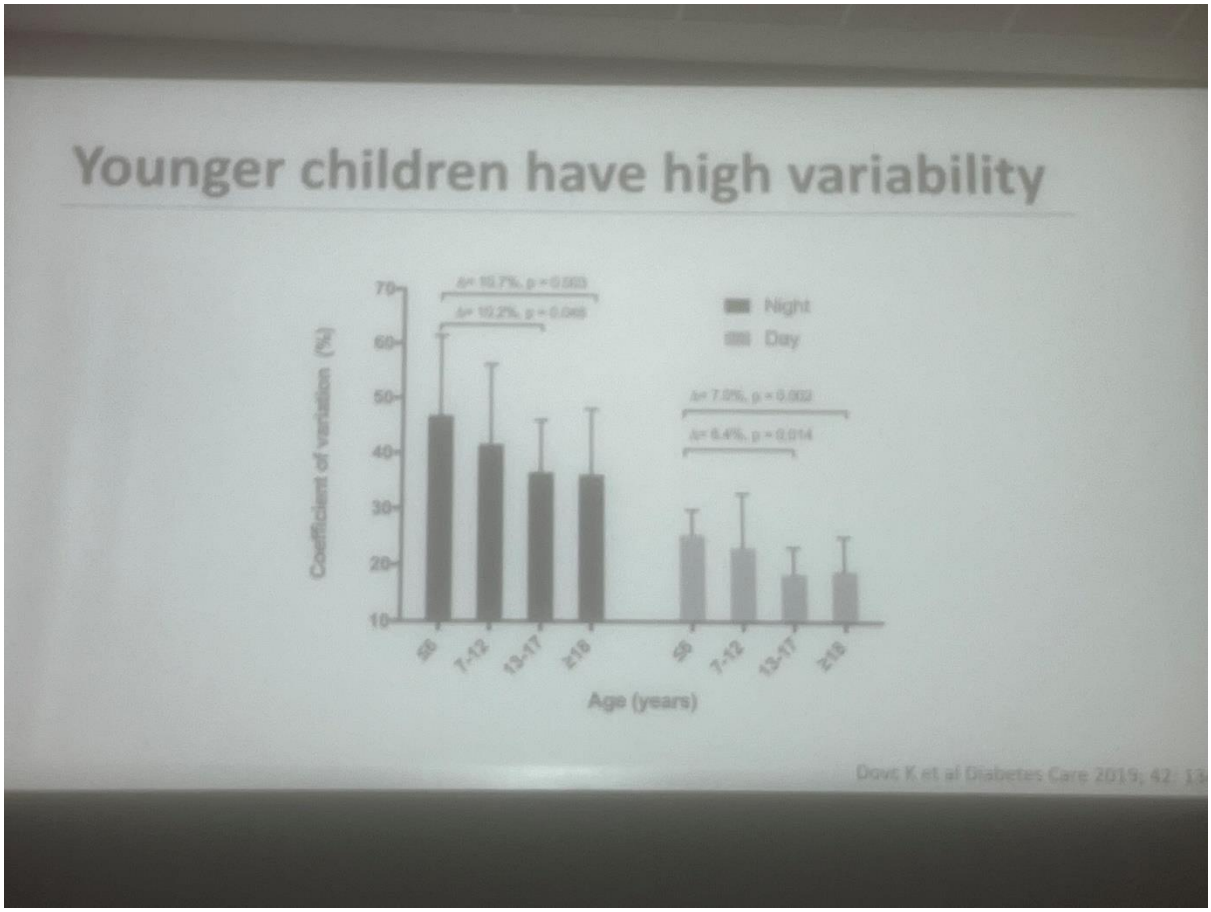
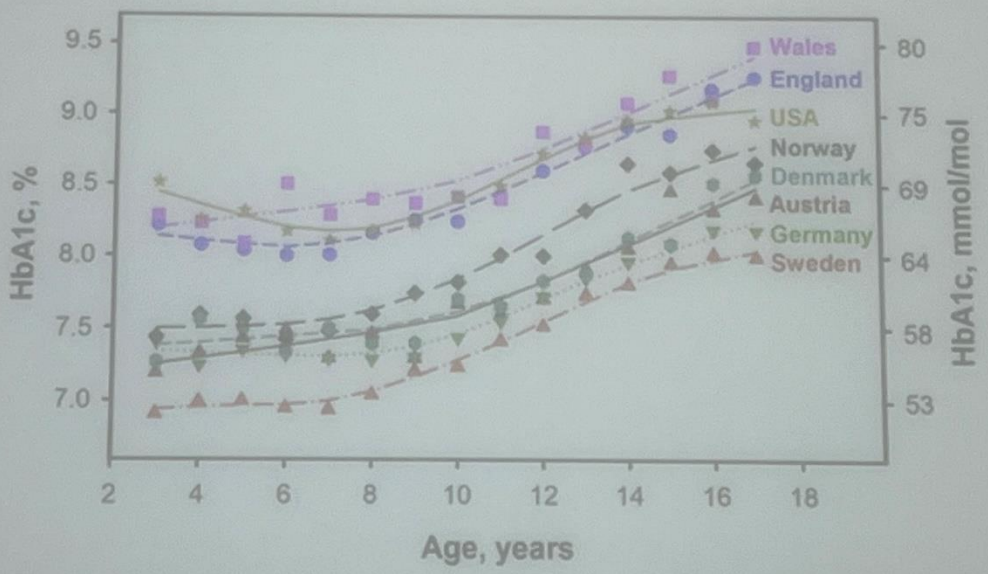


The 'tricky' years



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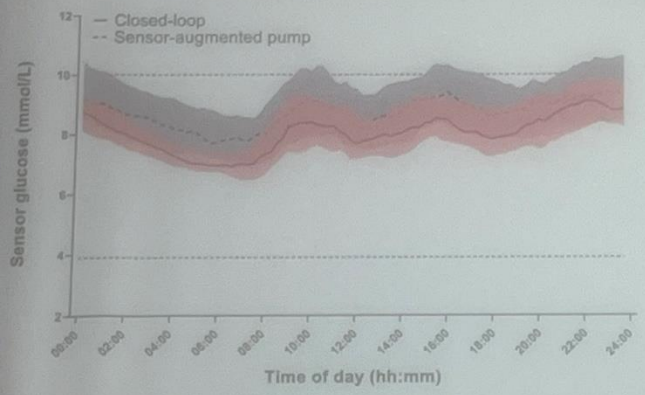
CamAPS FX algorithm RCTs

Acronym	Duration	Very young children	Children	Adolescents	Adults	Seniors	Preg
APHome04 Ph2	28 days				●		
APCam11	12 weeks		●	●	●		
KidsAP01	21 days	●					
Dan05	6 months		●	●			
KidsAP02	16 weeks	●					
APHome04 Ph3+4	8 weeks				●		
CLOuD	2 years		●	●			
Dan06	16 weeks					●	
FAST-Kids	8 weeks	●					
Clip03 + Clip24/7	28 days						
AiDAPT	Pregnancy						
TOTAL		3	3	3	4	1	

Closed-loop in very young children



- N=74, 1-7yrs, multi-national
- 16 weeks, crossover design
- Baseline HbA1c 57mmol/mol

Hy
se

- **Results:**
  - Time in range +9%
  - HbA1c -0.4%
  - Time <3.9mmol/L no diffe
  - Mean glucose -0.7mm

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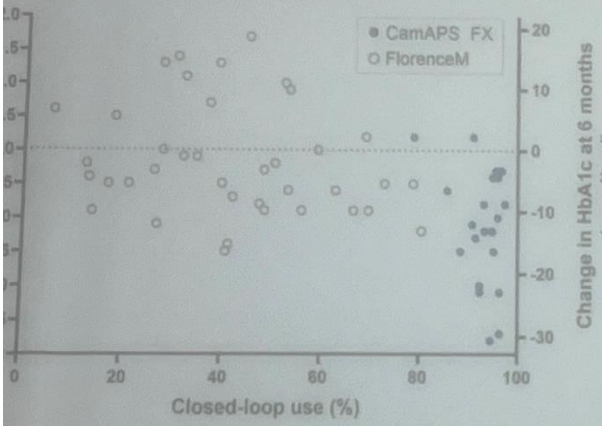
Closed-loop in children & adolescents cont



- 6-month RCT
- Closed-loop vs pump +/- sensor
- n=133, 6-18 years (12-centre USA
- CamAPS FX (n=46), FlorenceM (n=87
- Baseline HbA1c 8.2%

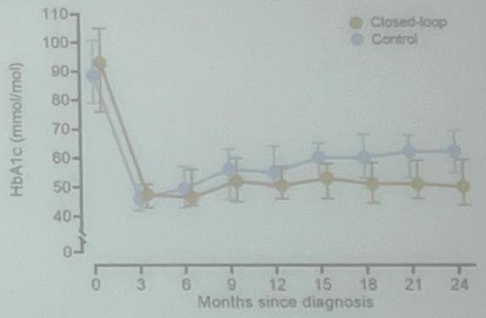
- **Results CamAPS FX cohort (n=45):**
  - Time in range +15 percentage p
  - HbA1c -1.05 percentage
  - Mean glucose -2mmol/L
  - Time <3.9 no change

Ware J & Boughton CK et al. Lancet Digit Health. 2

Closed-loop from onset of diabetes

- n=97
- Age 10-16 years
- Recruited within 21 days of diagnosis
- 1:1 randomisation; 24 months
- Multicentre

Hybrid closed-loop
vs standard care



Results

- C-peptide AUC ↔0.06pm
- Time in range +14%
- HbA1c -1.0%
- Mean glucose -1.7mmol/

urtesy of Dr CK Boughton

Boughton CK et al. N Engl J

Real-world data

	Overall	≤6 years	7-14 years	15-21 years	22-64 years
Users (n)	1805	214	203	95	820
Observation period (days)	84.0 (54.0, 118.0)	95.0 (61.0, 122.0)	84.0 (55.5, 117.0)	77.0 (47.5, 116.0)	88.0 (58.0, 124.0)
Age (years)	30.2 ± 19.3	3.8 ± 1.5	10.3 ± 2.2	17.3 ± 2.0	41.4 ± 10.9
Mean glucose (mmol/L)	8.4 ± 1.1	8.8 ± 1.1	8.5 ± 1.1	8.7 ± 1.2	8.2 ± 1.1
Glucose SD (mmol/L)	3.1 ± 0.7	3.4 ± 0.7	3.3 ± 0.8	3.5 ± 0.9	2.9 ± 0.7
Glucose CV (%)	36.2 ± 5.5	38.7 ± 4.5	38.9 ± 5.5	39.5 ± 5.9	35.1 ± 5.1
GMI (%)	6.9	7.1	7.0	7.1	6.9
Percentage of time with glucose					
3.9-10.0 mmol/L	72.6 ± 11.5	66.9 ± 11.7	70.5 ± 10.4	68.9 ± 11.2	74.2 ± 11.3
>10.0 mmol/L	24.7 ± 11.8	29.7 ± 12.0	26.3 ± 10.7	28.5 ± 11.5	23.3 ± 11.8
>13.9 mmol/L	5.2 (2.5, 9.4)	7.9 (4.2, 13.4)	7.1 (3.9, 10.5)	8.6 (4.6, 13.7)	4.3 (1.9, 7.8)
<3.9 mmol/L	2.3 (1.3, 3.6)	3.0 (1.8, 4.5)	2.9 (1.8, 4.3)	2.2 (1.3, 3.5)	2.1 (1.1, 3.3)
<3.0 mmol/L	0.4 (0.2, 0.7)	0.5 (0.3, 0.9)	0.5 (0.3,0.9)	0.4 (0.2, 0.7)	0.3 (0.1, 0.6)
Total daily insulin (U/day)	37.3 (20.8, 53.2)	11.2 (7.6, 16.0)	30.8 (21.7, 43.3)	55.9 (43.4, 76.6)	42.8 (29.9, 62.3)
Time using closed-loop (%)	94.7 (90.0, 96.9)	95.6 (92.6,97.1)	93.9 (89.0, 96.4)	93.2 (84.5, 95.0)	94.9 (90.4, 96.9)

John's thoughts:

1. The data supporting Automated Insulin Delivery (AID) is robust, and managing young children and adolescents can be particularly challenging.
2. Initiating AID treatment from the time of diagnosis might be a beneficial approach to enhance control, create a positive long-term impact, and lessen the overall burden. While it may not be suitable for individuals who prefer not to have a device on their body, it can be a valuable option for the majority.

ISPAD Day 3

Value-based healthcare focuses on improving the quality of care and outcomes for individuals with Type 1 Diabetes (T1D). On average, people with T1D have a shorter life expectancy, with those maintaining A1c levels above 64 mmol/mol living 13 years less. For those with A1c levels below 48 mmol/mol, the reduction in life expectancy maybe less severe, ranging from 4 to 7 years? The traditional metric used for over 50 years to model healthcare costs has been HbA1c, but this approach doesn't account for the impact of non-severe hypoglycaemic episodes.

To achieve continuous improvements that lead to world-class results, the healthcare team should operate like a Formula 1 racing team, similar to Diabeter. This involves:

- Clearly defined roles for team members, each highly trained in their respective areas.
- Shared vision among all team members, focusing on improving the quality of life and glucose control.
- An iterative approach involving Planning, Execution, Auditing, and Continuous Improvement.
- Embracing change as the norm, as stagnation leads to stagnation in results.
- Adhering to a philosophy that includes setting ambitious goals (e.g., having everyone on Automated Insulin Delivery by December 2024 with a median A1c below 55 mmol/mol).
- Establishing clear goals with accountable lines of responsibility.
- Challenging existing models to determine if change is necessary.
- Ongoing self-learning within the team, sharing knowledge gained from conferences, conducting regular audits, and using the information to improve.
- Fostering an environment where ideas are challenged rather than individuals, promoting constructive discussions and feedback.

To differentiate follow-up care:

Once everyone is on a cloud-based system, regularly pull data and prioritize patients based on specific criteria:

- Patients with high Time Below Range (TBR) (>4%) should be the top priority for intervention.
- Individuals experiencing a rapid decline in Time in Range (TIR) by more than 20% in a week should be contacted promptly.
- Those using Auto mode less than 70% of the time require quick attention.

- Patients with low TIR (<50%) should also be a priority.
- Patients with >50% Time in Range and low TBR (<4%) who maintain consistency may not need immediate intervention.
- By implementing these strategies, the healthcare team can provide more effective care for individuals with T1D, improving their overall quality of life and glucose control.

John's thoughts on improving our diabetes team:

1. Establish a clear vision that encompasses our target median HbA1c, the overall quality of life we aim to improve, and a culture of continual improvement.

2. Cultivate a culture of ongoing improvement, encouraging experimentation, safe failures, and rapid learning. This might entail:
    a. Allocating dedicated time to challenge our existing models.
    b. Framing our challenges as discussions about ideas rather than personal attacks, ensuring that our language is understandable and non-personal.
    c. Holding individuals accountable for their own learning and providing opportunities for growth.

3. Continuously question whether our current activities align with our vision or if we're merely doing them out of habit. We must assess if our actions are the most effective use of our time to achieve our goals.

Insulin Thermoregulation

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(23)00028-1/fulltext

This study focused on the stability of insulin when stored outside refrigeration during the summer in India. The results indicated that acceptable insulin concentrations were maintained for up to 2 months for all samples of various insulin preparations. At 4 months, most samples, including analogue and human insulins, still had a relative concentration of 95% or more, meeting the safety criteria of the US Pharmacopeia which requires insulin potency to be 100 IU/mL (±5%).

Nuclear magnetic resonance testing did not reveal any loss of relative concentration. These findings align with a previous study by Kaufman and colleagues, which showed similar preservation of insulin concentration under different temperature conditions.

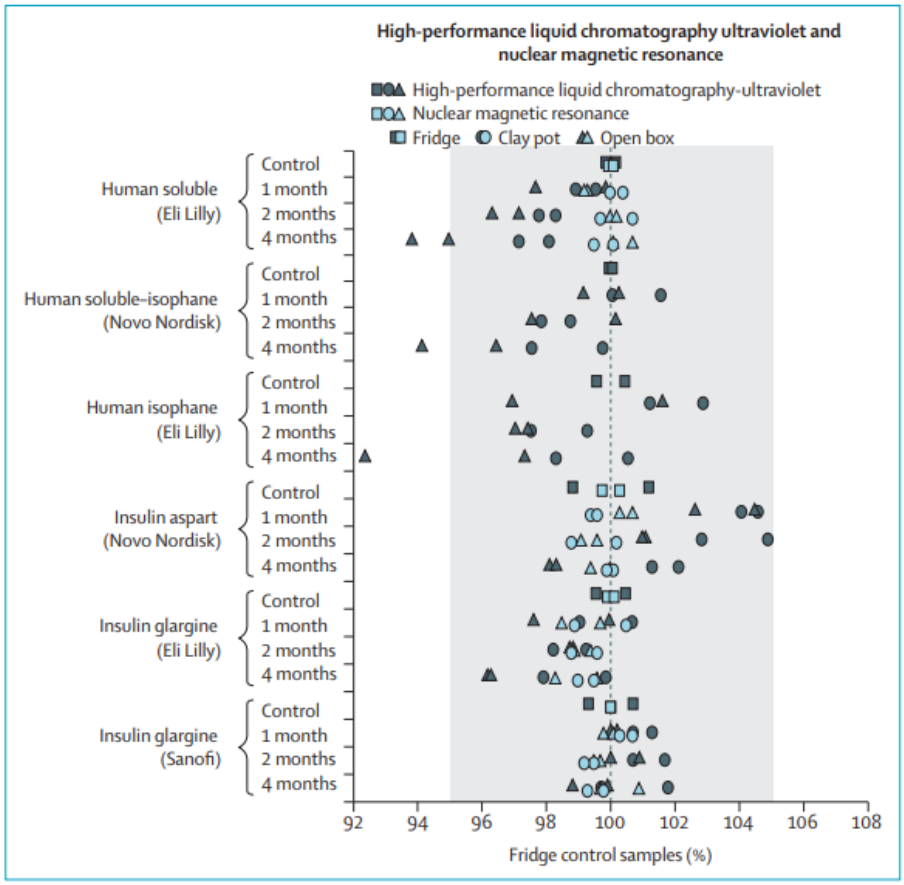


Figure: **Relative potency and total concentration of insulins at each timepoint**
Relative potency measured by high-performance liquid chromatography-ultraviolet (shaded in black), and relative concentration measured by nuclear magnetic resonance (shaded in blue), of the control insulins after storage in refrigerator (squares), and insulins stored in clay pots (circles) or boxes (triangles) for 1, 2, or 4 months. Nuclear magnetic resonance analysis was done at the University of Gothernburg and liquid chromatography-ultraviolet analysis at the University of Florida.

However, it's essential to acknowledge the limitations of this study, including the small sample size, the re-refrigeration of samples after storage in open boxes or clay pots, and the

lack of in vivo testing for changes in glucose concentration. Further studies are needed to understand the exact nature of insulin preservation under these storage conditions.

If these results are confirmed in larger real-world and laboratory studies, along with additional in vivo and biochemical tests, regulatory agencies may reconsider the recommendation to dispose of unrefrigerated insulin after only one month at room temperature (20–25°C). This could potentially extend insulin usage to 2–4 months in situations where daily temperatures cycle between 25°C and 35°C and refrigeration is unavailable. This change could reduce costs, waste, and anxiety among families regarding insulin effectiveness and safety.

Furthermore, it could provide valuable guidance to health professionals and improve insulin access in under-resourced settings. In many countries, traditional methods like clay pots and evaporative cooling techniques are used to keep insulin cool, with clay pots being especially effective in low-humidity conditions. This study supports the use of such basic devices by demonstrating that clay pot storage can help maintain insulin potency and reduce its decline.

John's thoughts

1. We don't have to be concerned about insulin being stored outside the fridge for up to 28 days. For analogues, it appears that up to 4 months is perfectly acceptable.
2. I had a conversation with the study authors, and it appears that data is showing good potency for 6-12 months, even at temperatures as high as 33 degrees Celsius (UK never gets this high).
3. This information alleviates concerns for families and reduces unnecessary prescriptions.
4. When we go on holidays, it's likely that we won't need to carry cool bags for insulin storage.
5. As this new data emerges, it's important for us to reconsider our thinking and practices regarding insulin storage.

DeDoc session

DeDoc session on approaching consultations with a person with T1D, consider:

1. Thank you for joining us today.
2. What would you like to achieve from this session for it to be beneficial?
3. I have some topics to cover, but let's start with any concerns or topics you'd like to discuss.
4. Before making any decisions based on the data we have, let's discuss and collaborate. Decisions are made together.
5. No one is perfect in following every guideline, so let's approach this with understanding and compassion.

T1D Oral Session

Gut microbiome and low carb diet

- <80-130g (age dependent) per day or less than 25%
- Prospective cross-over 5 weeks
- 20 patients HbA1c 48 mmol/mol at baseline
- 95g vs 193g per day with more fat and protein in the
- Mixed results on gut microbiome
- ? controlled for fibre intake.
- Does change gut microbiota but awaiting results to see the impact

GMI and POC HbA1c

- 90-day Dexcom GMI and A1c >70% - Dexcom G6
- <22yrs t1D
- 1051 youth – 6 yrs - ? NHW 82% - NHB 6%
- POC 7.3% - 7.7% = 0.4% difference r=0.78
- No ethnic sub-analysis
- A1c is more dynamic with adolescent and 90-days maybe too long?

Does A1c benefit those with High A1c:

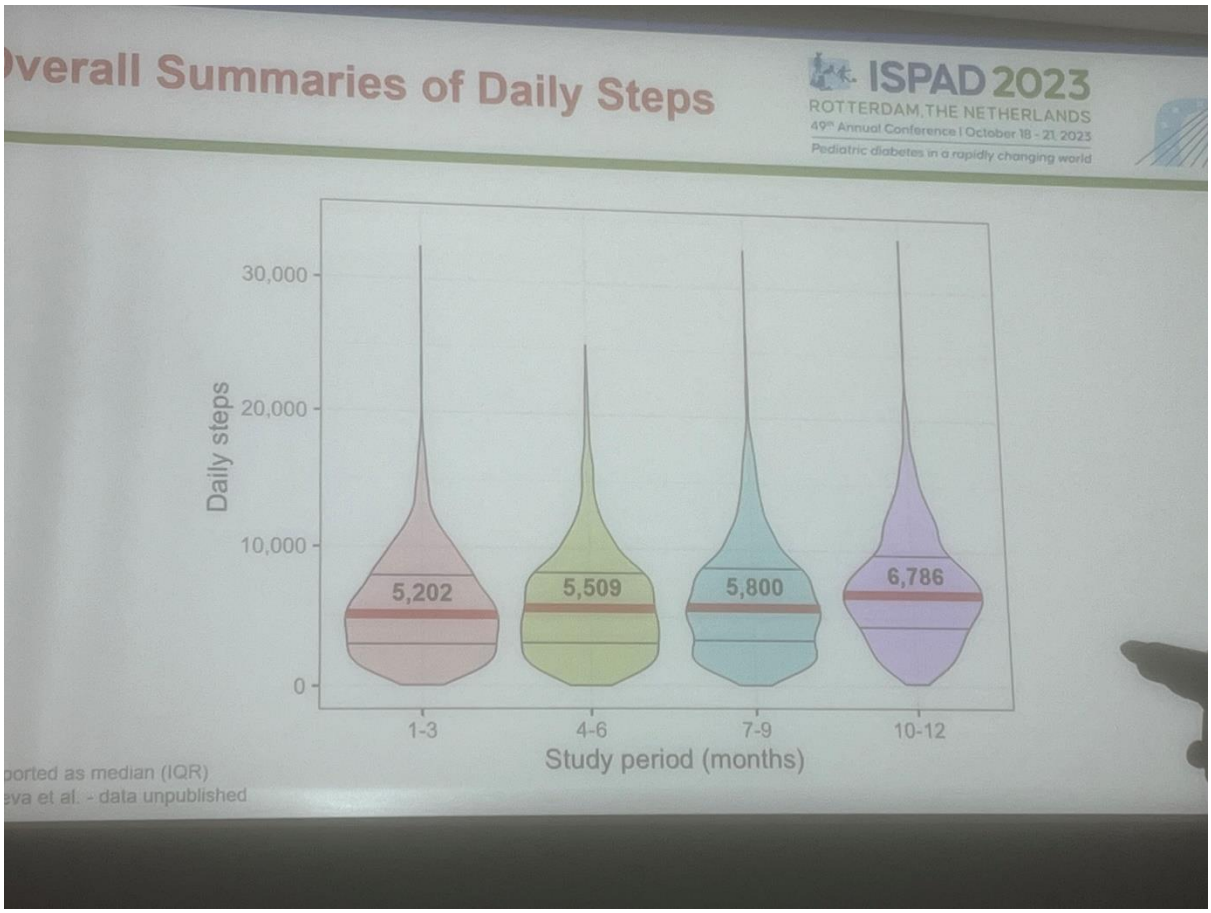
- HCL vs SAP in poorly controlled
- A1c >8.5% 12-25 years
- 4 centres
- 42 – 21 in each arm
- 8.8% vs 9.9% - 0.8% drop in favours of HCL
- 19% TIR and 12% TITR
- No change in psychosocial measures
- Only 50% usage of HCL

GRI predicts T1D self-management habits in youth.

- Few studies on GRI in youth and in particular self-management
- T1D > 1yr
- CGM and insulin pump
- >50% wear time
- 3 of 7 components as a minimum
- Mixed effects model due to multiple participants
- N=1487 – 84% white
- Strong relationship

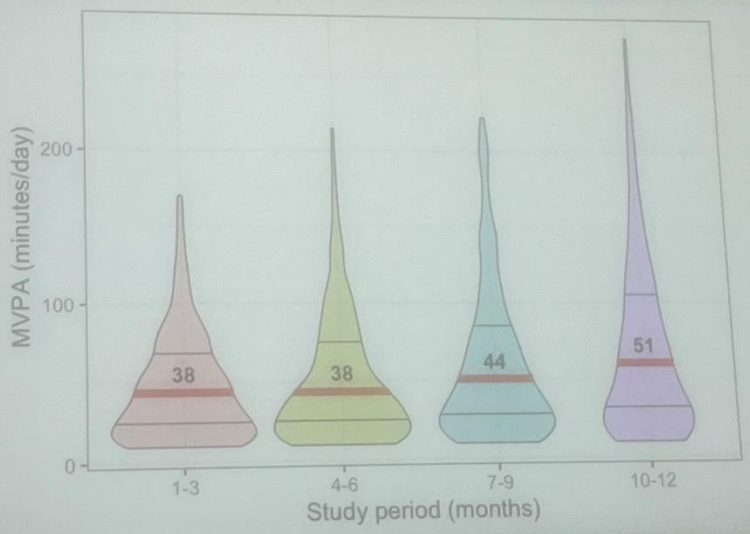
Increasing step count during first year of diagnosis in youth with T1D

- Activity tracking + 4 telehealth sessions
- Reduce barriers to exercise
- CGM within one month of diagnosis
- See activity buckets
- >10,000 steps, slightly higher step count



Overall Summaries of Moderate-to-Vigorous Physical Activity (MVPA)

ISPAD 2023
ROTTERDAM, THE NETHERLANDS
49th Annual Conference | October 18 - 21, 2023
Pediatric diabetes in a rapidly changing world



Moderate and High Daily Steps Associated with Higher TIR

ISPAD 2023
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Pediatric diabetes in a rapidly changing world

Bi-hormonal fully closed loop in adolescents:

- 12-18yrs 6 months after diagnosis with A1c <97 mmol/mol
- 14 days cross over of fully closed loop vs open loop
- 8 vs 7 (lost 20-30% of patients)
- MARD 16.3% so did not use the Dexcom data
- Not a non-inferiority study

Anti-viral for enterovirus – DiViD Study:

- RCT of getting Anti-viral vs not – given twice weekly for 26 weeks
- C-peptide stimulation is the end-point.
- Diagnosed within 3 weeks for first injection age 6-16 yrs
- No differences in groups at baseline (n=47 treatment) (n=49 Placebo)
- 1 year primary end-point
    - Faster decline in c-peptide in control group (p=0.37)
    - More treatment group with C-pep >0.2pmol

John's thoughts:

1. Combine CGM data and HbA1c to evaluate risk.
2. Aim for 10,000 daily steps as a family goal.
3. HCL is safe and effective for teenagers with high A1c.
4. Bi-hormonal treatments involving Glucagon might not be commercially feasible.
5. Anti-viral treatment holds some promise in prolonging the honeymoon at 12 months

ISPAD – Day 4

Issues and Management of Young Children's Food Behaviour:

1. Peer influence is paramount for young children.
2. Between the ages of 2-6, food neophobia (fear of new foods) is common and is a typical developmental phase.
3. Young children pose significant challenges because they:
    - Have limited vocabulary to express themselves.
    - Exhibit minimal emotional stability.
    - Display unpredictable activity levels.
    - Are prone to illnesses.
    - Demonstrate inconsistent insulin sensitivity.
4. Children under 7 years have a 41% Time in Range (TIR) with a 4% Temporary Basal Rate (TBR) as per "Diabetic Medicine" (refer to the provided picture).
5. Parents' primary concerns, as illustrated in the graph, include low blood sugar levels during their child's sleep.

Key Recommendations:

1. Foster positive feeding habits in parents:
    - Refrain from restricting food.
    - Introduce new foods up to 15 times.
    - Avoid pressuring children to eat.
2. Encourage family meals:
    - Parents should model a positive attitude towards food.
    - Ensure a stress-free meal environment, which can be challenging due to diabetes-related concerns.
3. Maintain a health-focused home food environment by:
    - Exposing children to a variety of healthy foods.
    - Emphasising the joy of eating.
4. Cultivate open communication with families, allowing them to share their practices and concerns.
5. Recognise the importance of parents getting adequate sleep, which AID can assist with, ensuring they remain patient and attentive.

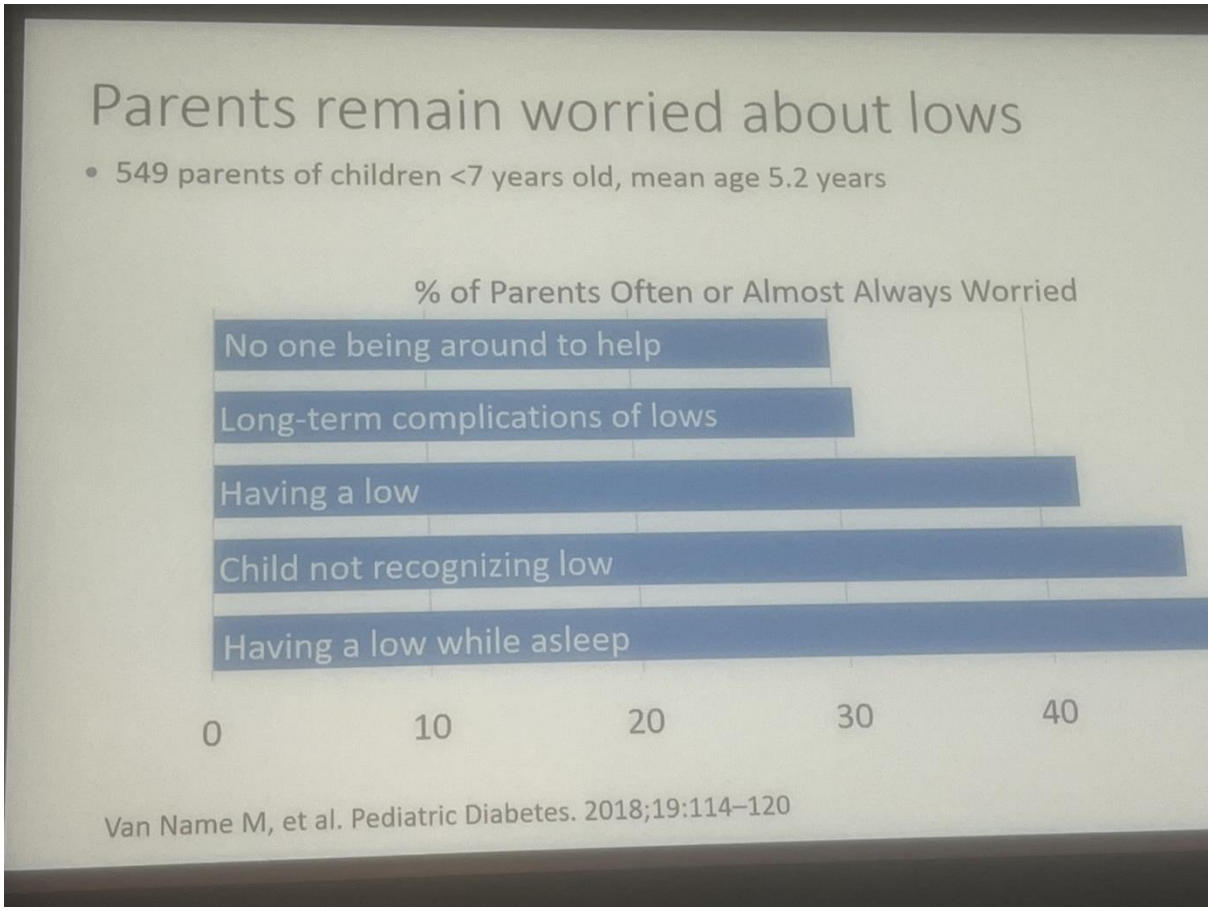
Challenges of Type 1 Diabetes (T1D):

1. Carb counting.
2. Administering insulin injections.
3. Aligning carbohydrate intake with insulin doses.
4. Anxiety over hypoglycaemia (low blood sugar).
5. Concerns about hyperglycaemia (high blood sugar).
6. Stress during mealtimes.
7. The time and financial constraints associated with preparing healthy meals.

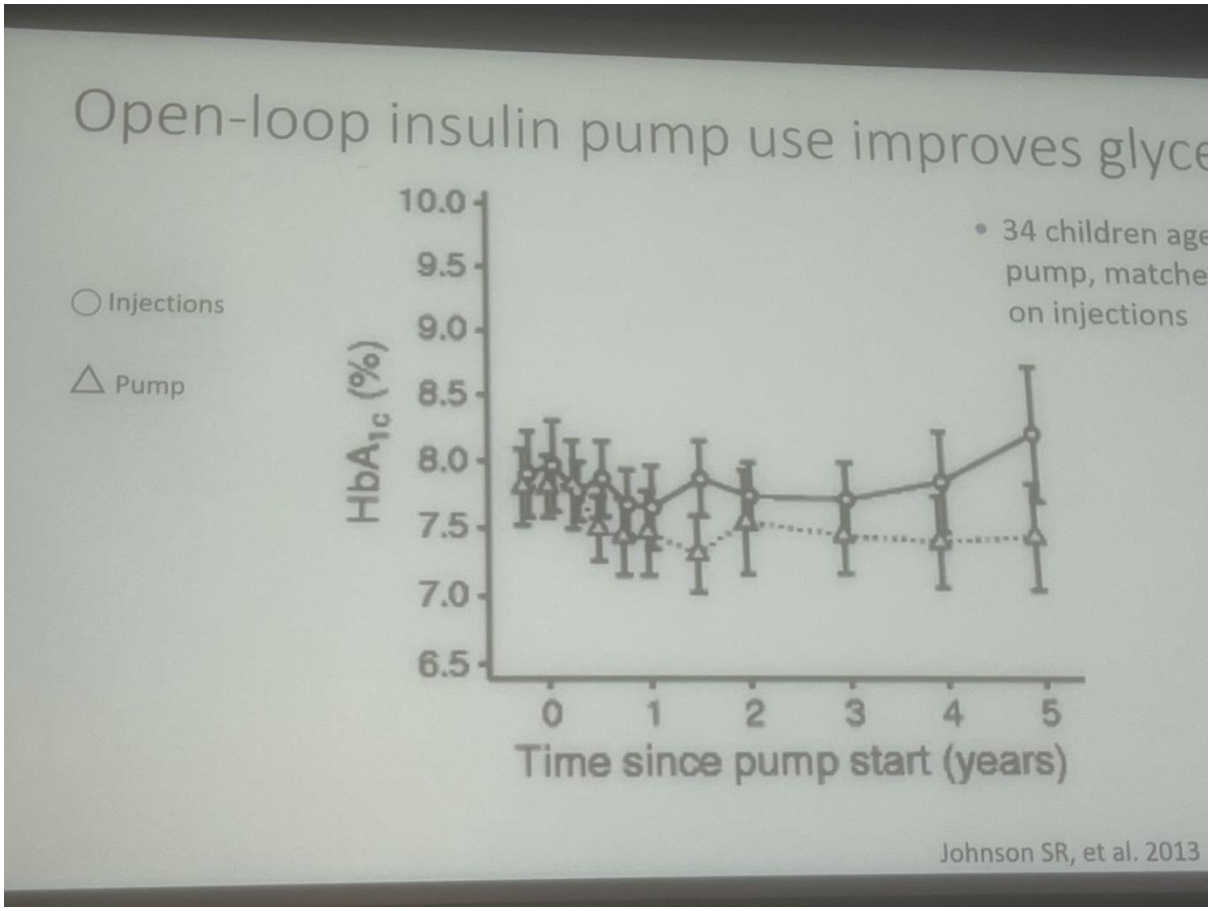
Coping Strategies:

1. Positive coping methods include:
    - Intervention programmes.
    - Positive reinforcements.
    - Prioritising family meals.
    - Setting clear rules.
    - Consistent meal timings.
    - Utilising diabetes technology like dual wave insulin delivery.
    - Pre-bolusing approximately half of the insulin dose.
    - Employing Automated Insulin Delivery (AID) systems.
    - Having readily available healthy backup foods.
2. Some maladaptive bolus (insulin dosing) strategies that may emerge:
    - Relying on backup foods like ice cream.
    - Avoiding certain foods, e.g., pizza and pasta.
    - Creating self-devised bolus strategies.
    - Compromising on healthy eating habits.

Michelle Van Name – Technology and eating behaviours



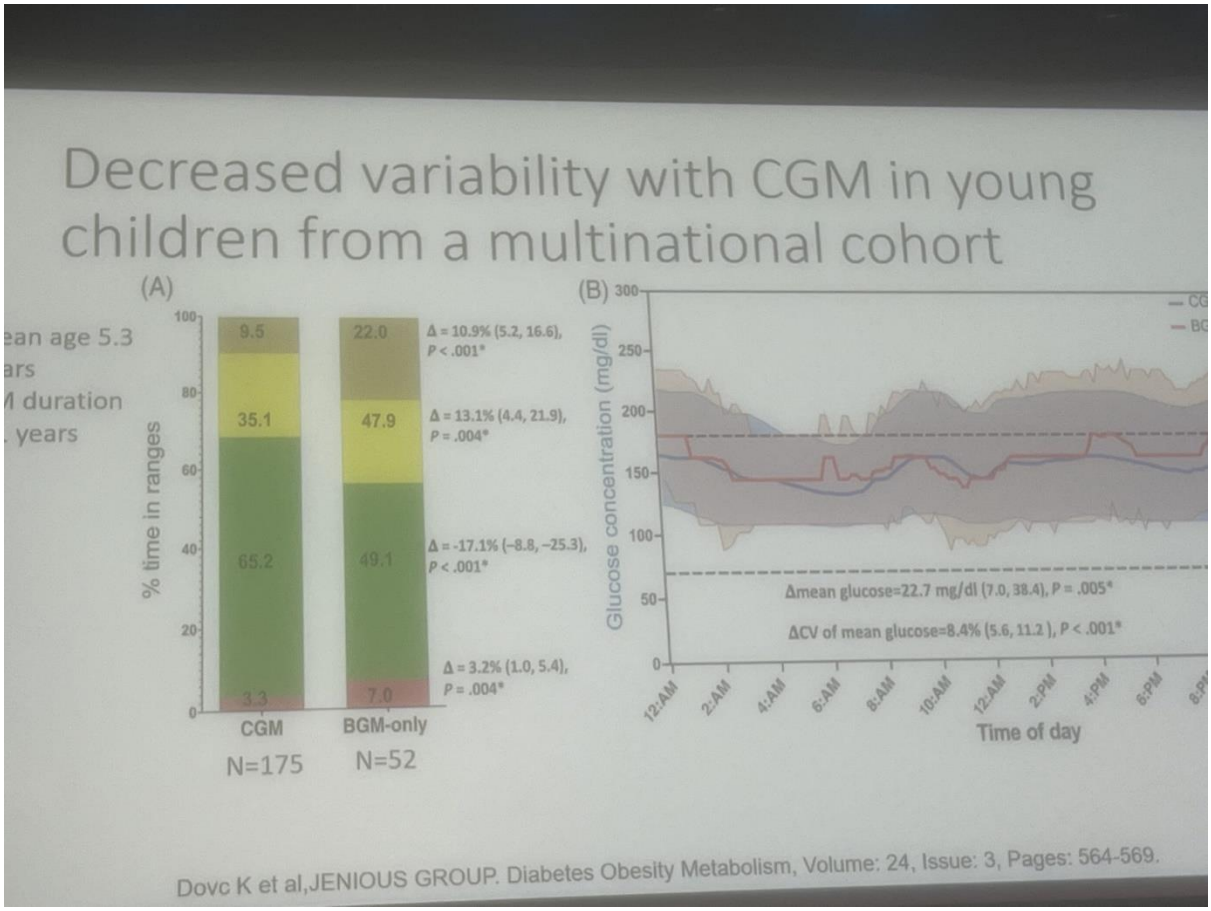
Pumps beat injections



This is why.

- Small frequent bolus's – 50% upfront
- Remote boluses from the phone
- TBR
- IOB to prevent stacking
- Dual wave bolus's
- Need good backpacks, belts, clothing with pockets etc
- Lock screens
- 2-part adhesion sets

CGM in young children



CGM placement to prevent compression lows

Stress for parents with continual monitoring

Skin solutions booklet needed

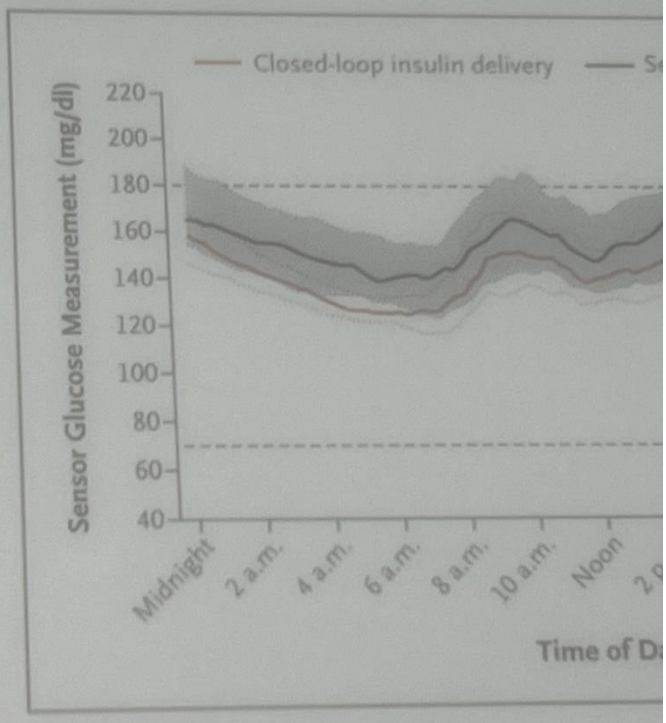
AID is needed due to high variability in insulin requirents

RCTs shows AID is the winner for both CamAPS FX and Control-IQ and 780G and real-world data

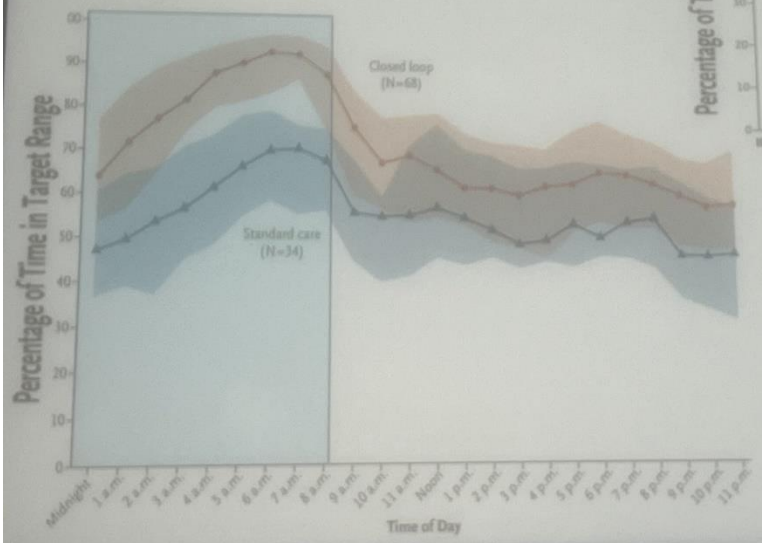
AID in Young Children – RCT Crosso

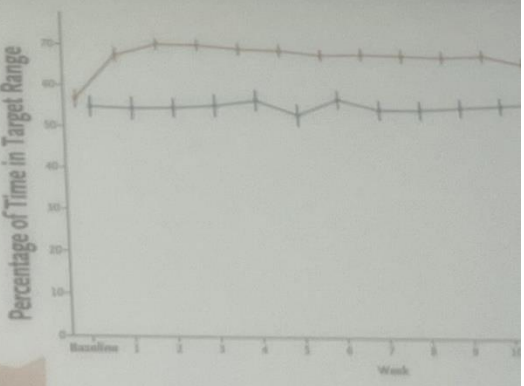
-74 kids
-Age 1-7, mean 5.6 years
-Randomized to 16 weeks of CamAPS AID or SAP, then switched
A1c 7.3 before study

With AID
-95% Time in Automation
-Time in Range ↑ 8.7%* to 71.6%
-Time in Hyper ↓ 8.5%*
-Time in Hypo did not ↑
-HbA1c ↓ 0.4% (3.9 mmol/mol)



AID in Young Children - RCT



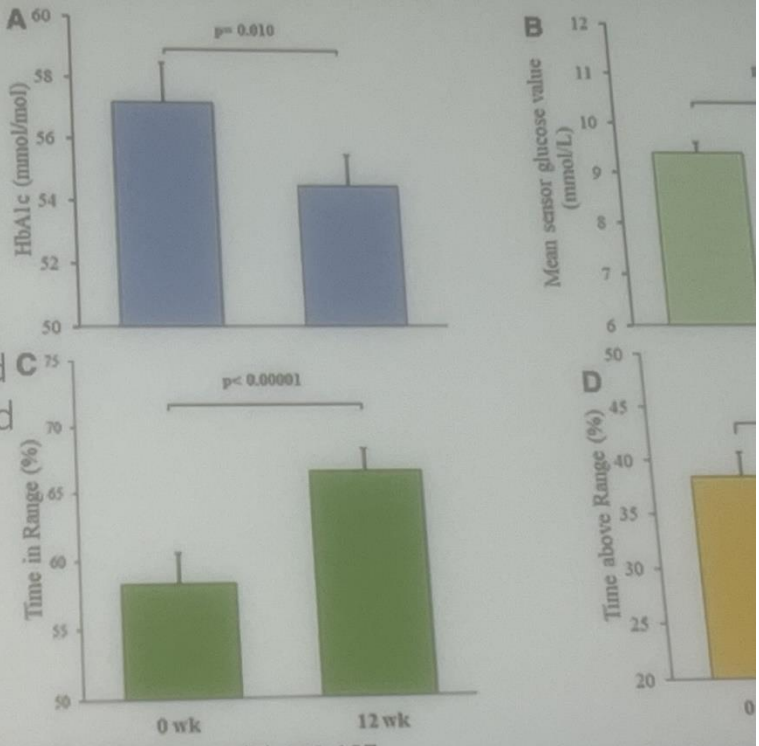


-102 kids
-2- 5 years of age
-Randomized 2:1 to AID (Cont
Standard care with pump or i
CGM x 13 weeks
-Mean A1c at baseline
7.5% (AID) & 7.7% (Stand

RP Wadwa et al. N Engl J Med 2023;

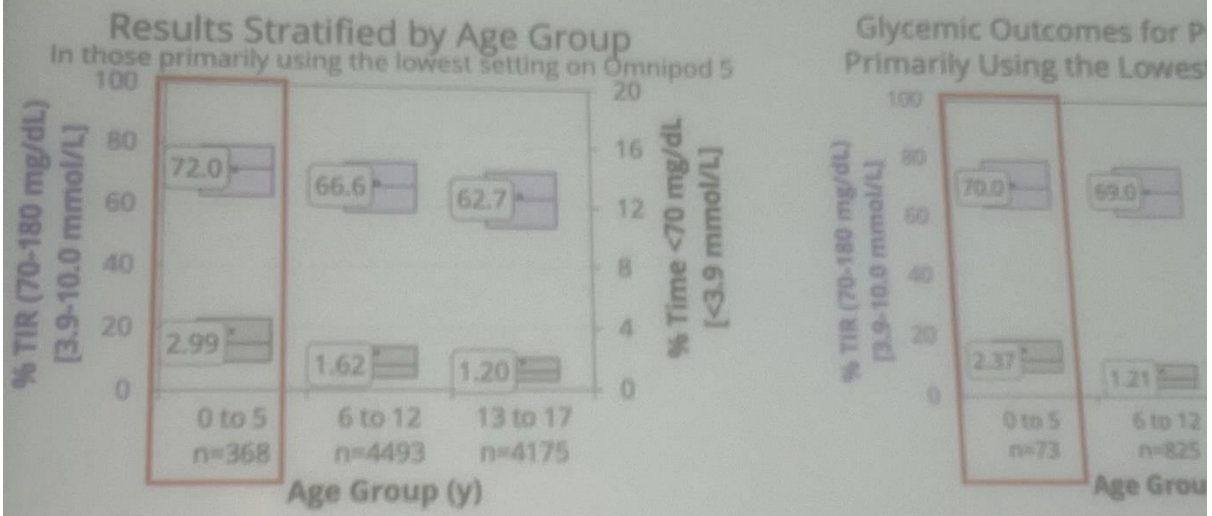
AID in Young Children - Pre/Post

35 kids age 2-6 years
12 weeks on Minimed 780G advanced hybrid closed loop



Pulkkinen MA, et al. Diabetes Technol Ther. 2023 Feb;25(2):100-107.

Real world AID data in Preschoolers



Jennifer L. Sherr, et al. Real-World Glycemic Outcomes of 22,240 Children and Adolescents with Type 1 Diabetes Using the Omni (AID) System with Cloud-Based Data Management. **Poster Number P-094, ISPAD 2023**

Features that are helpful for young children

System	Minimum Requirements per Regulators
CamAPS FX	Total Daily Dose 5 units
Control IQ	Total Daily Dose 10 units
Minimed 780G	Total Daily Dose 8 units
Omnipod 5	Total Daily Dose 5 units
iLET	Age 6+

Anticipatory Guidance:

- Avoid late bolusing for carbohydrates
- May need to adjust treatment for low if insulin delivery is suspend

Parent reported outcomes improved with AI

- Children age 1-7 years
- In random order, had two 4-month periods of either AID o
- Surveys at baseline and after each treatment

able 1—Descriptive statistics for measures for different treatment arms

	Baseline (N = 74)	HCL period (n = 73)[a]	SAP period (N = 74)	Adjusted me difference (95%
FS total score[c]	72.4 (14.9)	64.6 (12.6)	68.9 (12.7)	−5 (−9, −
FS-behavior subscale score[d]	35.4 (5.9)	33.4 (5.8)	34.9 (6.6)	−2 (−3, −
FS-worry subscale score[c]	36.9 (11.2)	31.2 (8.7)	34.2 (9.2)	−3 (−6, −
S total score[e] Caregiver Sleepiness	6.1 (4.1)	5.6 (3.8)	6.5 (4.3)	−1 (−2,
HO-5 total score[d] Wellbeing Index	69.3 (16.6)	75.0 (17.8)	66.6 (18.4)	8 (3, 1

de Beaufort C, et al. Diabetes Care. 2022 Sep 16;45(12):3050–3.