

ESPE 2018 SATELLITE SYMPOSIUM

MEETING REPORT

Insulin Treatment & Advanced Technology in the Management of Children with Diabetes

With Professor Francesco Chiarelli & Professor Tadej Battelino

Saturday 29th September 2018 at 08:00–08:45
Athens Megaron Conference Centre



MANAGEMENT · MONITORING
PAEDIATRIC AND ADOLESCENT
DIABETES

 Springer Healthcare IME

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INTRODUCTION

This satellite symposium is part of the “Management and Monitoring of Paediatric and Adolescent Diabetes” (MMPAD) programme, a European-wide set of independent educational activities, organised by Springer Healthcare IME, for healthcare professionals managing children and adolescents living with type 1 diabetes.

This symposium offered an opportunity to learn from the experts best practice for insulin treatment and how current and emerging technologies can help to improve glycaemic control.

We hope that you find this meeting report useful and that it will support you in keeping on top of the latest advances in this rapidly evolving field.

LEARNING OBJECTIVES

- Discuss best practice for the implementation, individualisation and modification of insulin treatment
- Debate how current and emerging technologies can improve glycaemic control

EXPERT FACULTY



Francesco Chiarelli

Programme Director and Symposium Chair
Professor and Head of Paediatrics, Department of Paediatrics,
University of Chieti, Italy



Tadej Battelino

Consultant and Head of Department,
Department of Pediatric and Adolescent Endocrinology,
Ljubljana University Medical Centre, Slovenia

UPDATE ON INSULIN TREATMENT FOR CHILDREN WITH DIABETES

Chiarelli began his presentation with a reminder that the prevalence of type 1 diabetes is currently on the rise, with about half a million children affected worldwide and an additional 85,000 cases diagnosed every year.

He described type 1 diabetes as a sword of Damocles, hanging over the heads of children, because of the increased risk of microvascular and macrovascular complications.

And the underlying processes leading to beta-cell destruction and diabetes remain unclear, Chiarelli stressed, saying that although our understanding of the pathogenesis has increased over recent years, “we don’t know the beast that kills the beta cells”.

With that incomplete understanding in mind, he advised the audience to “be humble” and to reconsider a type 1 diabetes diagnosis if, for example, the required insulin dose remains low after many years.

Chiarelli gave a reminder of the internationally agreed staging for type 1 diabetes, with stage 1 defined as positivity for one or more islet autoantibodies, and stages 2 and 3 defined by the onset of asymptomatic and symptomatic hyperglycaemia, respectively.

Treating these children is no straightforward matter, because not only do insulin needs vary throughout the day, but insulin sensitivity decreases markedly during puberty, accounting for 30% of children’s basal insulin needs. Insulin sensitivity varies even within a 24-hour period, increasing at night and thereby raising the risk for hypoglycaemia.

Other factors, such as food intake and physical activity, also influence children’s insulin requirements, creating a narrow therapeutic margin, and it is very difficult to replicate physiological production of insulin, not least because it must be delivered subcutaneously, increasing the required dose. Also influencing choice of insulin regimen are issues such as the child’s age, duration of diabetes, their lifestyle, and personal and family preferences, as well as their physician’s preferences.

Chiarelli reminded the audience that a “conventional” regimen, still to some extent used in developing countries, comprises up to five insulin injections per day, not necessarily timed to meals, whereas modern insulin treatment is based on basal insulin with bolus injections adjusted for carbohydrate intake. A basal-bolus regimen is much more physiological than a conventional regimen, he noted, but also more complex to manage.



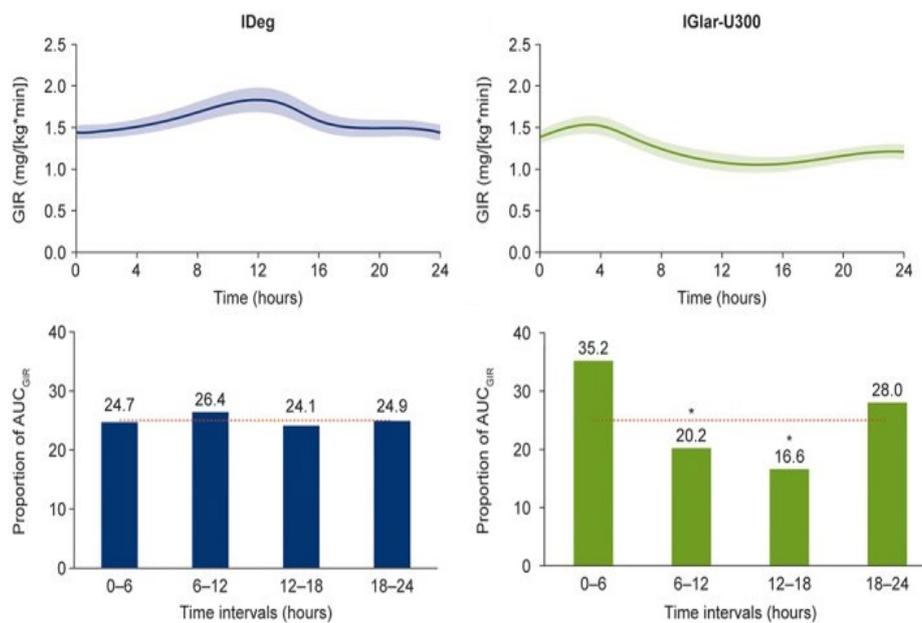
An extract from Prof Chiarelli’s presentation is available here

The goals of insulin treatment are to reduce the time in hypoglycaemia and hyperglycaemia, and the degree of glycaemic variability, said Chiarelli. “And let me reiterate here that hyperglycaemia is as risky as hypoglycaemia. For decades we had thought that the main issue was hypoglycaemia, but now we know that hyperglycaemia is also dangerous for the brains of the children, particularly young children”.

He added that glucose variability “is our enemy”, being damaging to the brain of the child in the short-term, as well as contributing to long-term complications.

Chiarelli then gave an overview of the currently available insulins. Discussing the newest preparations in more detail, he noted that the two longest-acting insulins – glargine U300 and degludec – have very similar effects on glycaemic control, with both having a relatively constant release rate into the blood rather than a distinct peak time when their concentration is highest.¹

Recent Long-Acting Insulins



And turning to the latest in short-acting insulins, he noted topline, not-yet-published results showing that faster-acting insulin aspart is “efficacious and safe” when compared with NovoRapid® in children and adolescents with type 1 diabetes.

“So I think that we as paediatricians should say that insulin treatment in children is easier today”, said Chiarelli.

“Of course education is paramount from the very beginning”, he added, and also reminded the audience of the need to regularly check injection sites and patients’ techniques and skills.

THE LATEST TECHNOLOGIES FOR TYPE 1 DIABETES

Battelino opened his presentation by highlighting a “crucial paper”, recently published in *The Lancet*,² showing reduced survival in patients with type 1 diabetes – by an average of 17 years in patients diagnosed within the first 10 years of life.

The paper also showed a particularly high cardiovascular mortality risk in females with diabetes, mostly strikingly for myocardial infarction, and in line with other findings.

“And my first message for today: we need to understand why”, said Battelino.

However, he highlighted a “window of opportunity”, stressing that the increased mortality risk for patients with diabetes affects only those with poor glycaemic control. And he raised the issue of poor glucose control during puberty, saying: “We actually just accept this [...] I don’t believe this should be accepted so easily.”

As Chiarelli did, Battelino noted the evidence that brain damage in children with diabetes is related not, as previously believed, to severe hypoglycaemia, but rather to glucose variability and to hyperglycaemia.

These day-to-day fluctuations in glucose levels are not reflected in patients’ glycated haemoglobin (HbA1c) levels, however. So while HbA1c is very useful as benchmark of glycaemic control across centres and countries, Battelino believes it is no longer a helpful indicator in clinical practice.

For example, a study published in *The BMJ* showed virtually identical average HbA1c levels between insulin pump users and patients on multiple daily injections, yet mortality was significantly lower in the pump users.³ A separate study showed significantly reduced rates of microvascular complications in pump users⁴ and a *JAMA* paper reported reduced rates of hypoglycaemia, diabetic ketoacidosis and severe diabetic ketoacidosis, despite only a very small difference in HbA1c relative to injection users.⁵

“So please be aware that having A1c as the major or primary outcome is probably not the best idea”, said Battelino, because of the “considerably larger” benefits that may be overlooked when relying on a marker of average glucose levels to gauge the effectiveness of a treatment.



An extract from
Dr. Battelino’s
presentation is
available here

Battelino’s group recently showed that poor glycaemic control in children with type 1 diabetes is associated with significant shortening of telomeres, the protective caps at the end of the chromosomes – a phenomenon more usually associated with ageing.⁶

The increasing importance of glucose variability highlights the value of continuous glucose monitoring (CGM), which reveals the day-to-day fluctuations that are concealed by HbA1c, allowing patients to target them. As a consequence of reducing hypoglycaemia, CGM also demonstrably increases the time patients spend within an optimal blood glucose range.

Another intervention for improving time in range is an insulin pump augmented with a function that suspends insulin delivery for when the patient's blood glucose falls below a predetermined threshold, or even when blood glucose is predicted to fall below a certain level. As demonstrated in the ASPIRE and PROLOG trials, for instance, this reduces hypoglycaemia and consequently increases time in range.^{7,8}

So CGM is becoming the standard of care, said Battelino, because of its important benefits even when used standalone, in patients using multiple daily injections. Other benefits include improvements in hypoglycaemia awareness and improved quality of life related to a reduced frequency of hyperglycaemic events.

Moreover, the CONCEPTT study showed that CGM use by pregnant women with type 1 diabetes improved their time in range and resulted in a significant reduction in the proportion of babies born large for their gestational age.⁹

Battelino noted the recent arrival of sensors that are implanted subcutaneously, can last for 6 months and have a mean absolute relative difference (MARD; between monitor readings and actual capillary blood glucose) below 10%, predicting that the diabetes technology "landscape will be considerably changed" as a result.

And although these technologies are more expensive than conventional means of blood glucose monitoring, Battelino cited an analysis of the RESCUE trial,¹⁰ which suggested CGM may be cost-saving at a national level due to reductions in diabetes-related hospital admissions and work absences.

The first closed-loop system, also known as the artificial pancreas, was approved in the USA in 2016, and several other companies have systems undergoing development and testing. In clinical trials, the amount of time patients spend in auto (ie, closed-loop) mode correlates with the amount of time they spend in range. Closed-loop systems have been tested in pregnant women, children and during exercise.^{11,12}

But the long developmental process of these devices has resulted in patients creating their own versions, using already available pumps and CGM devices, controlled by open-source algorithms.

"I am not sure how safe this is, but it shows the imminent need people with diabetes have to reduce the burden of their condition", said Battelino.

Finally, noting that CGM produces a vast amount of data that can be difficult and time-consuming to interpret, he introduced the concept of advisor apps. One example is the DreaMed Advisor Pro, an app with which Battelino is personally involved*, which gives insulin dose advice based on CGM readings. When the team tested it against multiple experienced clinicians, the decisions of the app differed from that of the clinicians by no more than the clinicians' decisions differed from each other.¹³

Battelino says that for doctors without immediate access to a diabetes specialist, "you simply click the button and within less than a second you have your suggestion", on how an expert might advise the patient to adjust their treatment. The advisor is currently the subject of a multicentre clinical trial, he said.

Summing up, Battelino reiterated the importance of preventing cognitive impairment, and the issue of poor outcomes in females with type 1 diabetes. "I believe it is time to act".

In response to a comment from an audience member, he also emphasised the importance of glycaemic control in even very young children. "No matter how small the child is, we should strive to have the glucose within target or very close to it".

And Chiarelli pointed out that, despite the adverse effects of hypoglycaemia in the very young achieving recent prominence, its effects on the risk for micro- and macrovascular complications was in fact demonstrated in a study published in the 90s.

He believes that children should be started on insulin pumps as early as possible, a point with which Battelino concurred. "Whatever it takes: I couldn't agree more."



An extract from
the Q&A session
with Prof Battelino
is available here

* Professor Battelino owns stocks in DreaMed Diabetes.

REFERENCES

1. Rosenstock J, Cheng A, Ritzel R, et al. More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial. *Diabetes Care* 2018; 41: 2147-54.
2. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* 2018; 392: 477-86.
3. Steineck I, Cederholm J, Eliasson B, et al. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study. *BMJ* 2015; 350: h3234.
4. Zabeen B, Craig ME, Virk SA, et al. Insulin Pump Therapy Is Associated with Lower Rates of Retinopathy and Peripheral Nerve Abnormality. *PLoS One* 2016; 11: e0153033.
5. Karges B, Schwandt A, Heidtmann B, et al. Association of Insulin Pump Therapy vs Insulin Injection Therapy With Severe Hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes. *JAMA* 2017; 318: 1358-66.
6. Tesovnik T, Kovač J, Hovnik T, et al. Association of Glycemic Control and Cell Stress With Telomere Attrition in Type 1 Diabetes. *JAMA Pediatr* 2018; 172: 879-81.
7. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia. *N Engl J Med* 2013; 369: 224-32.
8. Forlenza GP, Li Z, Buckingham BA, et al. Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial. *Diabetes Care* 2018; 41: 2155-61.
9. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017; 390: 2347-59.
10. Charleer S, Mathieu C, Nobels F, et al. Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study. *J Clin Endocrinol Metab* 2018; 103: 1224-32.
11. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. *N Engl J Med* 2016; 375: 644-54.
12. Dovc K, Macedoni M, Bratina N, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. *Diabetologia* 2017; 60: 2157-67.
13. Nimri R, Dassau E, Segall T, et al. Adjusting insulin doses in patients with type 1 diabetes who use insulin pump and continuous glucose monitoring: Variations among countries and physicians. *Diabetes Obes Metab* 2018; 20: 2458-66.

FURTHER INFORMATION

Educational Grant

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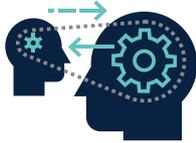
Organiser

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As a member of the Good CME Practice Group, Springer Healthcare IME creates and delivers independent education in compliance with European CME standards and codes of practice.

If you have any questions please do not hesitate to contact us at ime@springer.com

MORE ABOUT THE MMPAD PROGRAMME:



ROADSHOWS

European Roadshow

A collection of five meetings focusing on the diagnosis, management and possible prevention of diabetes in children, including both acute and chronic complications.

These meetings were held in Munich, Madrid, Milan, London and Paris involving leading local experts in the field of paediatric diabetes.



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CASE STUDIES

Interactive Patient Case Studies

- Renal Complications in Diabetic Ketoacidosis
- Maturity-onset Diabetes of the Young (MODY)
- Hypoglycaemia and technology

Authored by Professor Francesco Chiarelli

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