MANAGEMENT · MONITORING
PAEDIATRIC AND ADOLESCENT
DIABETES

EUROPEAN ROADSHOW

FRIDAY 29th JUNE 2018
MILAN, ITALY

An independent education programme for healthcare professionals managing children and adolescents living with type 1 diabetes

MEETING REPORT

CONTENTS

INTRODUCTION

The Monitoring and Management of Paediatric and Adolescent Diabetes (MMPAD) Roadshow is part of 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 expert-led day-long meeting in Milan offered attendees the opportunity to learn from the experts as well as share and discuss their own experiences in the diagnosis, management and possible prevention of the condition in Italy.

The programme covered acute and chronic complications, practical information about insulin treatment and the latest advances in technology used to treat young patients with type 1 diabetes.

We hope that you will find this meeting report useful, and that it will help further your understanding of the management and monitoring of paediatric and adolescent diabetes.

PROGRAMME

Morning sessions:

- Prediction and prevention of type 1 diabetes in children - Professor Francesco Chiarelli
- Diabetic ketoacidosis - Dr. Riccardo Bonfanti
- Hypoglycaemia - Professor Claudio Maffeis
- Chronic complications - Dr. Cosimo Giannini

Afternoon sessions:

- Practical insulin treatment - Professor Claudio Maffeis
- Advances in technology for diabetes treatment - Dr. Riccardo Bonfanti

LEARNING OBJECTIVES

Following this meeting, delegates will be able to:

- Estimate the risk of, and understand how to predict and possibly prevent, type 1 diabetes in children and adolescents.
- Assess the risks of, and effectively manage, acute and chronic complications of type 1 diabetes.
- Discuss the best treatment options, including new insulins and advanced technologies, for maintaining optimal glucose control.

EXPERT FACULTY

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Professor Claudio Maffeis
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PREDICTION AND PREVENTION OF TYPE 1 DIABETES IN CHILDREN

Presented by Professor Francesco Chiarelli - University of Chieti

Globally there are ~550,000 children with T1D and annually there are ~85,000 new diagnoses. Current estimates predict increases in incidence of ~3% per year. Diabetes can lead to serious acute and chronic complications including ketoacidosis, hypo- and hyperglycaemia, retinopathy, macrovascular complications, nephropathy and neuropathy, which in the long term can lead to disability and death.[1]

The pathogenesis of T1D is complex with the fundamental event being the destruction of pancreatic beta-cells via autoimmune reactions. However, what causes the immunological attack is not known, although there are several hypotheses being studied. These include the role of some viruses such as Coxsackie viruses, a reduced immunological tolerance linked to an altered activity of T-regulatory cells, and the implication of cytokines, such as IL-2 and IL-10.[2]

An extract from Professor Chiarelli 's presentation is available here

Reflection: It is possible to predict the onset of T1D

There are markers sufficiently reliable in predicting the onset of the disease: the most important are GADA and IA-2, and anti-insulin antibodies, particularly useful for the diagnosis of prediabetes in early childhood.

Fig. 1. Immunological markers of humoral autoimmunity against beta-cells

Glutamic acid decarboxylase autoantibodies (65kD isoform)	GADA
Tyrosine phosphatase related islet antigen 2	IA-2
Insulin autoantibodies	IAA
Zinc transporter 8	ZnT8
Islet cell antibodies	ICA

Skyler J et al., Diabetes 2009

It is important to know that the presence of autoantibodies is considered to be already an initial phase of T1D, in accordance with the indications of the JDRF (Juvenile Diabetes Research Foundation), the ADA (American Diabetes Association) and the Endocrine Society.

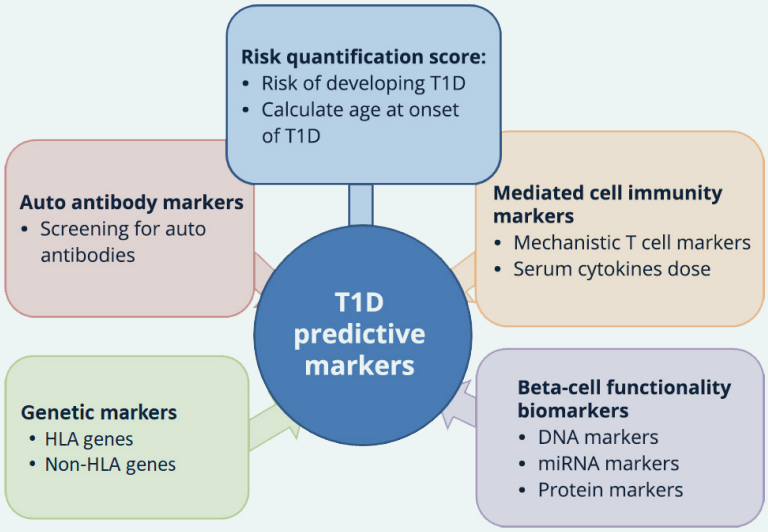
In fact, three stages are recognised in T1D, in which the autoimmune reaction towards beta cells is already present:[3]

- Stage 1: Blood sugar is normal, the patient has no symptoms
- Stage 2: Blood sugar is impaired when fasting or after eating, there are no symptoms yet
- Stage 3: Hyperglycaemia is present and the patient is symptomatic

Once stage three has been reached it is too late to prevent the disease. Recognising the disease in its earliest stages allows ketoacidosis to be avoided and an intervention to take place while there is still the possibility of preserving remaining beta cells.

Reflection: Predicting T1D is possible thanks to the different emerging biomarkers

Fig. 2. T1D predictive markers



The most reliable genes in predicting the risk of T1D are still the HLA (especially DR3 / DR4); insulin genes (INS) are also indicative of a significantly increased risk, albeit less than HLA. In children between 3 and 10 years, the presence of anti-islet autoantibodies correlates highly with the risk of developing T1D and, in particular, the presence of 3 antibodies greatly increases the risk compared to the presence of 1-2 antibodies[4,5]

Preventing the onset of T1D

So far, efforts to prevent T1D have been very disappointing, with many excellent trials not providing the desired results. Prevention strategies should be stage-specific, based on the prevention of autoimmunity in stage 1 with the addition of beta-cell preservation in the prediabetic phase. In newly developed diabetes the focus should be on glycaemic control, while in full-blown disease it is appropriate to focus on the prevention of complications.[6] Why has prevention not worked? The causes are many and include: the still limited understanding of the pathogenesis and heterogeneity of T1D; the costs of screening; the difficulties of validating markers and identifying molecules able to stop the progression of the disease; and the failure to optimise preventive combination therapies. Immunotherapy

may be nonspecific, directed against T and B cells, cytokines or co-stimulatory molecules (they act as anti-CD3, abatacept and teplizumab, against CTLA4-Ig still abatacept, and as anti-CD20 rituximab), or antigen-specific (ASI), based on the administration of autoantigens (insulin, GAD65, MonoPepT1De, MultiPepT1De). There are also many combination therapy options, including anti-inflammatory agents (such as anti-IFN and anti-TNF), immunomodulators, autoantigens and beta-cell preservers (such as GLP1-receptor agonists). The real problem is to adequately characterise the children to be treated. Future perspectives focus on characterising young patients and the design of "tailor-made" studies that could perhaps succeed in prevention, where previous approaches have failed.

DIABETIC KETOACIDOSIS

Presented by Dr. Riccardo Bonfanti - San Raffaele Hospital, Milan

Epidemiology and diagnosis

Diabetic ketoacidosis (DKA) is defined, according to the ISPAD 2014 guidelines, as: [7]

- hyperglycaemia (> 200 mg/dL)
- venous pH <7.3 or HCO3- <15 mmol/L
- ketonaemia >3 mmol/L
- presence of glycosuria and ketonuria.

It may be mild (pH <7.3 or HCO3- <15 mmol/L), moderate (pH <7.2 or HCO3- <10 mmol/L) or severe (pH <7.1 or HCO3- <5 mmol/L). When DKA starts there is a spontaneous or induced reduction of insulin, which causes hyperglycaemia, ketonaemia, polyuria and polydipsia, dehydration and metabolic acidosis.

The epidemiology of DKA recognises a wide geographical variability – from 15 to 67% at onset and from 1 to 10% per year in diabetic patients; it has an inverse correlation with the incidence of diabetes. In Italy, the average incidence of DKA at the onset, for the period 2005-2012, is 40% and, despite the considerable work done to increase the sensitivity to the problem, it has not been possible to change it over time.[8,9]

An extract from Dr. Bonfanti 's presentation is available here

In many cases the condition is not diagnosed, so it has been suggested that a capillary blood sugar test be imposed on all children in the emergency room. In fact, DKA mortality (about 1 case/year in Italy in the period 2004-2013) and morbidity at onset is relatively high, which may include electrolyte disturbances, hypoglycaemia, disseminated intravascular coagulation (CID) and acute respiratory distress syndrome (ARDS), chronic renal failure, acute pancreatitis and rhabdomyolysis.[10,11] Neurological sequelae can also be important and permanent. If, as we have seen, it is difficult to prevent diabetes, DKA must be prevented.

Reflection: Key messages for DKA management

In the presence of a suspected DKA diagnosis, it is necessary to send the patient to specialised centres that are able to manage the situation.

The key recommendations for the management of DKA are:[11]

- modest rehydration (0.9% physiological solution, at a rate of 5-10 mL/kg/h), with careful monitoring of electrolytes (and not of blood sugar)
- modest amount of insulin for a slow glucose correction (no bolus)
- no bicarbonates
- monitor the patient attentively and pay particular attention to cardiovascular data
- monitor the possible occurrence of cerebral oedema.

Cerebral oedema is the most frequent cause of mortality and morbidity in DKA, with a prevalence of 0.3-1%, and is particularly common in preschool children. The diagnostic criteria are shown in the table below.

Reflection: Criteria for the diagnosis of cerebral edema in diabetic ketoacidosis (Rabbone et al., Acta Biomedica 2015)[11]

DIAGNOSTIC CRITERIA	MAJOR CRITERIA	MINOR CRITERIA
Abnormal motor or verbal response to pain	Altered state of consciousness	Vomiting
Decorticate or decerebrate posturing	Reduced heart rate (<20 beats / minute)	Cephalalgia
Paralysis of cranial nerves (especially III, IV and VI)	Incontinence	Lethargic state
Disturbed breathing (wheezing, tachypnea, Cheyne-Stokes breathing)		Diastolic pressure > 90 mmHg
Apnoea		Age < 5 years

The diagnosis, with 92% sensitivity and 96% specificity, is made by the presence of 1 diagnostic criterion or 2 major criteria or 1 major criterion and 1 minor criterion.

It is also fundamental to know the risk factors for cerebral oedema:[11]

- High creatininaemia at diagnosis
- Severe acidosis at onset
- Excessive and rapid alkalisation
- High levels of sodium corrected at the beginning of treatment
- Lack of sodium increase during treatment
- Hyperhydration in the first hours of treatment
- Rapid reduction of blood sugar and acidosis
- Insulin administration in the first hours of treatment

Management of cerebral oedema requires:[11]

- Start of treatment if diagnosis is suspected
- Administration of mannitol 18% ev, at a dose of 0.5-1 g/kg, in 20-30 minutes, with repetition after 2 hours if necessary
- ⅓ reduction of liquid infusion
- In case of non-response to mannitol, administer hypertonic saline solution (3%), 2.5-5 g/kg in 10-15 minutes
- Intubation and artificial ventilation, if necessary
- Cerebral CT scan, after treatment, to evaluate other possible causes (thrombosis, haemorrhage, cerebral infarction)

A recent work by Kupperman assessed the infusion of fluids in paediatric DKA, highlighting how neither infusion rate nor sodium content correlates with acute and chronic CNS complications, but modulating the infusion rate of liquids is important for correcting cardiovascular parameters.[12]

Prevention of DKA

It is essential to try to prevent DKA at three different levels: to prevent its onset, to prevent relapses and to prevent its consequences. This can be achieved through a robust treatment protocol; the experience of the doctor is also crucial in prevention. An experiment conducted in the province of Parma in the 1990s drastically reduced the incidence of DKA through an information campaign in schools and recruitment of a random selection of paediatricians who were given a blood glucose and glycosuria measurement kit, a copy of relevant guidelines and a reference telephone number.[13]

The ISPAD 2014 guidelines estimate the risk of secondary DKA in children with T1D at around 10% per year and recognise the following conditions as risk factors:[7]

- Failure to take insulin treatment
- Poor metabolic control or previous episodes of DKA
- Gastroenteritis with persistent vomiting and inability to maintain hydration
- Psychiatric disorders, including eating disorders
- Difficult or unstable family conditions (e.g. domestic abuse)
- Puberty and adolescence in girls
- Limited access to health services
- Insulin pump therapy (CSII) not used correctly (as only rapid or short-acting insulin is used in insulin pumps, interruption for any reason leads rapidly to insulin deficiency)

Reflection: Strategy for reducing recurrences of DKA

A correct DKA recurrence reduction strategy includes providing the patient and their family with correct instructions on CSII to:[14]

- measure ketonaemia at each episode of hypoglycaemia (ketonaemia is preferable to ketonuria)
- check the correct intake of insulin, especially:
    - for adolescent patients with eating disorders,
    - for people who lose weight, have a high BMI or high levels of HbA1c;
    - for people suffering from anxiety or depression or with difficult family situations.

It is important to provide the patient with clear rules and instructions, preferably in writing, and a phone number for future reference.

HYPOGLYCAEMIA

Presented by Professor Claudio Maffeis - University of Verona

Diagnosis of hypoglycaemia

The table below summarises the criteria for the definition of mild and severe hypoglycaemia in children and adolescents.

Hypoglycaemia in children and adolescents

Hypoglycaemia	Infants (0–30 days)	Children (1 month–11 years)	Adolescents (12–17 years)
Mild	<70 mg/dL*	≤70 mg/dL	≤70 mg/dL
Serious	Coma or convulsions requiring parental therapy	Coma or convulsions or neurological symptoms requiring parental therapy	Coma or convulsions or neurological symptoms requiring parental therapy or assistance of another person

* Non-diabetic hypoglycaemia in infants is defined as < 40 mg/dL blood glucose

ACTA Biomedica, 2018:89:1-34

Reflection: Signs and symptoms of hypoglycaemia

The signs and symptoms of hypoglycaemia are predominantly CNS, where there exists a condition of neuroglycopaenia:[15]

Autonomous	Neuroglycopaenic	Behavioural
Agitation	Lack of concentration	Irritability
Sweating	Blurred or double vision	Erratic behaviour
Tremors	Altered colour vision	Agitation
Palpitations	Hearing problems	Nightmares
Pallor	Mumbled speech	Inconsolable crying
	Reduced ability to make decisions and confusion	Non-specific symptoms
	Short-term memory problems	Hunger
	Vertigo and instability	Headaches
	Loss of consciousness	Nausea
	Convulsions	Tiredness
	Death	

Cerebral damage is a typical consequence of severe and recurrent hypoglycaemia with obvious macroscopic effects from the standpoint of anatomical pathology. Fortunately, in children there is higher compensatory brain connectivity.[16] It must be said, however, that from the epidemiological standpoint, severe cases of hypoglycaemia have steadily declined since 2002.

An extract from Professor Maffeis' presentation is available here

Risk factors for hypoglycaemia

The pathogenesis of hypoglycaemia resides in an imbalance between dietary carbohydrate (CHO) consumed, physical exercise, and the insulin dose administered.

Risk factors of hypoglycaemia include:[15]

- age under 6 years
- low levels of HbA1c
- lack of awareness of hypoglycaemia
- past episodes of severe hypoglycaemia
- long-standing diabetes.

Age is a major risk factor for high glycemic variability that characterises early childhood. Another critical age is that of adolescence, typically for irregular lifestyles and alcohol consumption.

Insulin therapy and hypoglycaemia

In terms of insulin therapy, regular insulin is preferred over rapidly-acting analogues, which are more physiological, but expose the patient to high peaks. New long-term analogues are also good (particularly glargine and degludec). Recently, infusion pumps with auto sensors have led to the rate of severe hypoglycaemia being halved, especially at night. These new technologies give positive and reproducible results, meaning it is no longer necessary to correct hypoglycaemia with food, a practice that still tends to disrupt the metabolic system.

Exercise and hypoglycaemia

Exercise has a strong potential impact on hypoglycaemia via:[17]

- increased glucose oxidative disposal
- increased insulin-sensitivity
- exhaustion of glycogen stores
- counter-regulatory hormone deficiency induced by physical exercise (and training level).

It is particularly difficult to quantify physical exertion in young children and, consequently, to correctly predict consumption and insulin dose. Other risk factors for hypoglycaemia may emerge in relation to physical activity and insulin therapy, such as:

- wrong insulin dose
- insulin injection site

- lack of information/instructions to the patient
- duration and intensity of physical activity
- quality of metabolic control
- stress.

To be fully informed, young patients with T1D and their families should understand:[18]

- the role and action of insulin
- the effects of muscular activity on blood glucose
- metabolic changes that are related to physical activity
- late hypoglycaemia
- suitable monitoring procedures
- signs and symptoms of hypo/hyperglycaemia
- methods for correcting hypoglycaemia.

Reflection: Prevention of hypoglycaemia in children/adolescents who play sports

You can prevent hypoglycaemia by adopting certain measures:[19]

- Adapt insulin schedule to physical/sport activity
- Decide the insulin dose reduction before exercise
- Decide on the type and amount of CHO to be taken depending on the type of exercise
- Keep a glucagon emergency kit available
- Consider the risk of hypoglycaemia and consider whether to reduce the basic insulin dose

As for the ingestion of glucose, it is good to keep to the maximum limit of 1.5 g CHO per kg body weight per hour of intense or prolonged exercise. Glucose should be in the form of glucose tablets or boiled sweets, biscuits, crackers, energy drinks or fruit juices, while avoiding chocolate, dairy products and crisps. The general recommendation to prevent hypoglycaemic episodes is to control glycometabolic alignment before exercise (glycaemia >250 mg/dL with ketosis → avoid exercise; about 300 mg/dL blood glucose without ketosis → exercise with caution; blood glucose around 100 mg/dL → take CHO), measure your blood glucose during effort and take CHO (but not lipids) for prevention and treatment of hypoglycaemia.[20]

CHRONIC COMPLICATIONS

Presented by Dr. Cosimo Giannini – University of Chieti

An extract from Dr. Giannini's presentation is available here

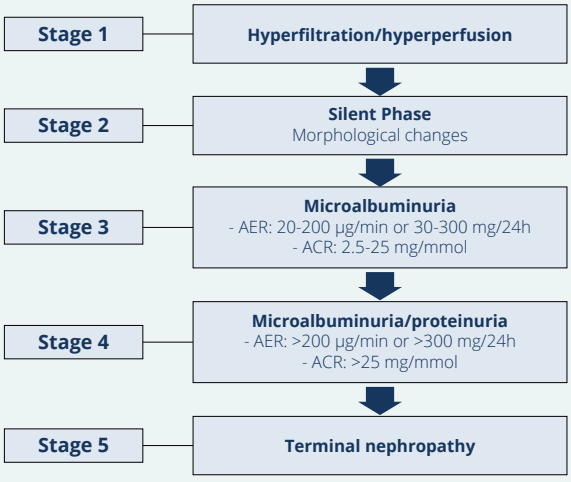
The chronic complications of T1D are vascular in nature and include diabetic neuropathy, retinopathy and nephropathy. There is also an increased risk of cardiovascular mortality of 2-4 times and stroke. The presence of one or more chronic complications of T1D in young patients results in nearly 60% deaths. The pathogenesis of vascular complications is complex and still not fully understood. Certainly the presence of micro- and macrovascular complications adversely affects the prognosis of T1D in children and adolescents.

Diabetic nephropathy (DN)

Its cumulative incidence ranges from 15 to 40% and is the main cause of end-stage renal failure, as well as a major cause of morbidity and mortality.[20]

Reflection: Clinical manifestations of diabetic nephropathy
Five stages of disease are recognised[21]

Fig. 3. Clinical stages of diabetic nephropathy



AER: albumin excretion rate; ACR: albumin/creatinine ratio

The earliest clinical manifestation of DN is microalbuminuria, the risk of which is related to HbA1c levels and duration of diabetes. Other risk factors of microalbuminuria during adolescence are female sex and puberty, hypertension, dyslipidaemia, smoking and GH/IGF-I axis imbalance in favour of GH. High glycemic variability represents an additional risk factor.

Research into new biomarkers of renal cell damage is being carried out through proteomics and metabolomics. Urinary cytokines/chemokines have been identified as markers of renal hyperfiltration in adolescents with T1D.[22] Emerging perspectives include the identification of biomarkers of glomerular (including albumin, transferrin, ceruloplasmin) or tubular (including α1 and β2 g-microglobulin) damage, oxidative stress and renal inflammation (including TNF-α, VEGF, IL-6).[23]

Screening for DN should start in children aged 10 years or at the beginning of puberty and in cases of diabetes of 2-5 years duration through evaluation of albumin/creatinine ratio (ACR) or albumin excretion rate (AER; ISPAD guidelines 2014 and 2018).

To control DN ACE inhibitors have been proposed to prevent the progression from microalbuminuria to proteinuria, although a recent trial demonstrated a non-statistically significant effect.

Diabetic retinopathy

Reflection: the four stages of diabetic retinopathy

1. Non-proliferative retinopathy with intraretinal microvascular abnormalities and bleeding
2. Pre-proliferative retinopathy with the addition of venous irregularities
3. Proliferative retinopathy with neoformation of vessels fed by retinal artery
4. Maculopathy with macular edema and hard exudates

The prevalence of retinopathy tends to increase with duration of diabetes and age and is higher in females. Other major risk factors for diabetic retinopathy are hyperglycaemia, hypertension, hyperlipidaemia, pregnancy and kidney disease; and to a lesser extent obesity, smoking, alcohol, and physical inactivity. Retinopathy screening should also be carried out on children from the age of 10 years with diabetes for 2-5 years, using fundus imaging or mydriatic ophthalmoscopy. Retinopathy prevention uses the usual microvascular complication prevention strategies in T1D: optimising glycaemic control, correction of lifestyles, blood lipid control and, above all, arterial pressure control.

PRACTICAL INSULIN TREATMENT

Presented by Professor Claudio Maffeis - University of Verona

The basic goal of insulin therapy is to try to mimic the physiology of the body, mimicking insulin secretion during meals and the basal insulinaemia of non-diabetic subjects. The mean values of HbA1c can be high during developmental years and subject to great variability in blood glucose.

An extract from Professor Maffeis' presentation is available here

The first objective is therefore to reduce glycaemic variability. The main available insulins are fast-acting analogues such as lispro, aspart and glulisine, and basal insulin analogues, such as glargine, detemir and degludec. NPH insulin is now little used. There is also a biosimilar to glargine insulin, abasaglar.

Reflection: Practical arrangements for the administration of insulin therapy

Since insulin administration schemes should mimic insulin levels in non-diabetics, in children, more than in adults, it is still preferable to administer regular insulin in the morning.

The characteristics of the needle and injection procedures are particularly important in children, which, after the first 2 years of age, have a lower subcutaneous fold than adults. Pen injectors are now also available for children. It is very important to reduce the risk of hypoglycaemia by ensuring that the injection is subcutaneous and not intramuscular: for this reason, 4 mm needles are used in paediatrics.

If the subcutaneous tissue is thin, a small puncture has to be carried out or the needle must be tilted at 45°.

The injection site should also be changed to avoid the risk of developing lipohypertrophy.

For very small patients or those with fear of needles, catheters in place for a few days are also available.

The 2014 and 2018 ISPAD guidelines provide a set of recommendations for the evaluation of the correct dose of insulin, which must take into account a number of factors related to the characteristics of the patient, their lifestyle and length and stage of diabetes.[24] In prepubescent children, generally, 0.7–1.0 IU/kg/day are required, while during puberty the dose may significantly increase to between 1.2 and 2 IU/kg/day. In the partial remission phase, however, the total daily dose of insulin is generally <0.5 IU/kg. Then there are situations of insulin resistance due to various factors, especially hormones, which require high doses of insulin.

The need for insulin has a direct relationship with CHO intake through diet. This has to be considered carefully, because CHO are present in almost every food type and can have different glycaemic indexes. It is important to assess the glycaemic index of the full meal and not on a single item of food. An accurate count of CHO and a better quality of diet improves glycaemic control and particularly HbA1c levels.[25]

Motivation, family support and the mental balance of the patients have a significant impact on metabolic control. Sometimes there are socio-psychological problems (anxiety, depression, eating disorders, family conflicts) that do not allow the patient to have the proper motivation to reduce factors of potential metabolic imbalance. In such cases, referral to a mental health professional with expertise in diabetes would be advisable.

The current availability of different insulin analogues, infusion pumps and continuous glucose monitoring offers the opportunity for children and adolescents with T1D to mimic the glycaemic profiles of non-diabetic subjects. However, a high level of information and education of patients and their families must be maintained to optimise the treatment of diabetes.

ADVANCES IN TECHNOLOGY FOR DIABETES TREATMENT

Presented by Dr. Riccardo Bonfanti – San Raffaele Hospital, Milan

Technology is now an integral part of diabetes therapy.

Reflection: Available technologies for the treatment of T1D

- The conventional therapies of multiple daily injections (MDI) and self monitoring of blood glucose (SMBG) are now reserved for patients who; have difficulty communicating with the referring doctor; do not have access to continuous glucose monitoring (CGM) or "flash" (FGM) system; and patients unable to properly use the information and/or existence of language/cultural/psychological barriers
- MDI multiple sensor for patients who are unable to carry an infusion pump, but are able to use a sensor
- Continuous subcutaneous insulin infusion (CSII) and SMBG are not recommended in children; rather it is preferable, although it is not the best solution, to use CSII with FGM for those who are capable of using it
- The Sensor Augmented Pump (SAP) represents the gold standard of insulin therapy in paediatrics and is indicated in the following patients:
  - <6 years at onset
  - with significant hypoglycaemic events
  - not in range for HbA1c
  - with high sensitivity to insulin
  - with neonatal diabetes
  - who are unable to use MDI daily
  - who do sport

An extract from Dr. Bonfanti's presentation is available here

FGM represents the input level of technology in diabetes and can provide much more information on SMBG. It is indicated for all patients with T1D aged 4-6 years and able to carry the device for more than 70% of the time. The FGM FreeStyle Libre is easy to carry, but has also a high variability. The Libre reduces hypoglycaemia by 30%. A study presented at ADA 2017 demonstrated a significant increase in glycaemic time range and a reduction of 1.5% (highly significant) in HbA1c when using the Libre system.

An extract from Dr. Bonfanti's presentation is available here

The ambulatory glucose profile (AGP) is an advanced application that summarises statistically standardised data on blood glucose, collected over a number of days, and displays them graphically. It has not seen a great deal of paediatric use. Forlenza et al[26] have used the software to process the data of the JDRF study, conducted in three age groups (8-14, 15-25, > 25 years) with HbA1c above and below the range, to analyse 1100 tracks from 393 patients. It was found that average blood sugar is different in different age groups, but always gets better in older subjects, while low blood glucose concentrations are lower in younger children and glycaemic variability is directly related to HbA1c levels.

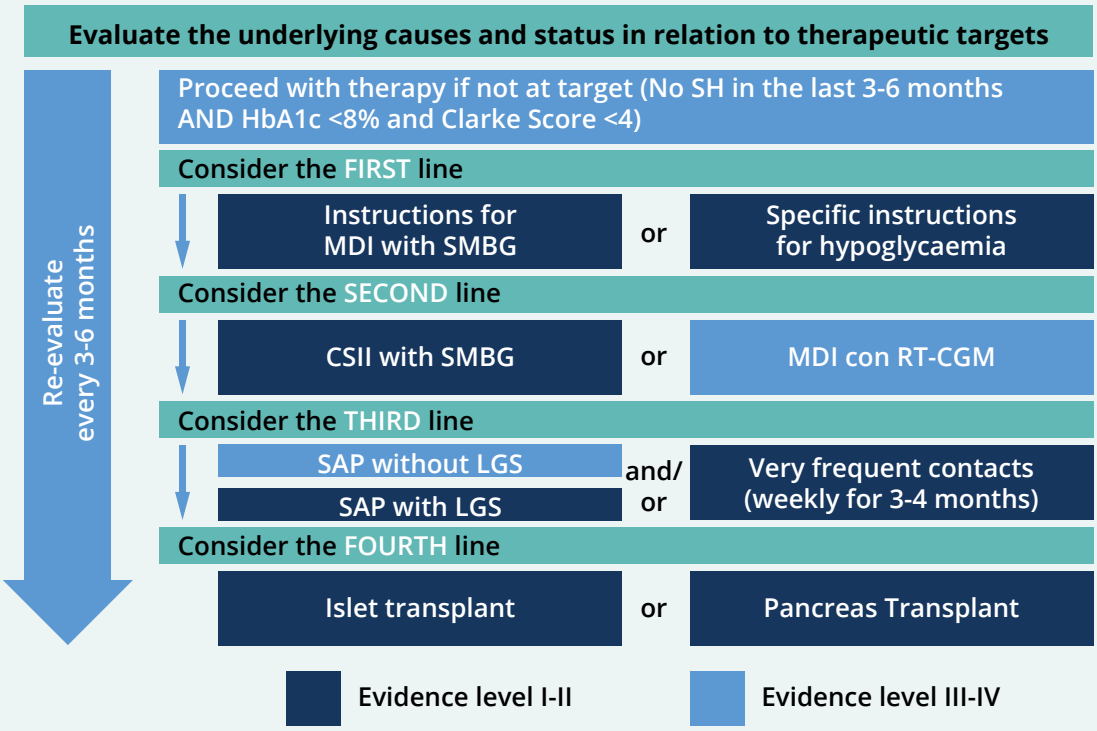
The CGM remains the most important tool in the management of diabetes and in the future will be the basis for the automatic release of insulin (AID). Cost effectiveness becomes favourable for two SMBG per day. It has been shown to reduce hypoglycaemia and HbA1c. It is indicated in all children under 6 years, in all patients with CSII, in those with low blood glucose concentrations or those who play sports that require remote monitoring. The REPLACE-BG trial has shown that CGM alone equals BGM + CGM, that there are no differences according to age, level of education or experience with CGM, and risks in terms of insulin dosage do not increase; the JMC has enabled a reduction of 52% in BGM, although BGM was still allowed for high risk situations.[27]

In summary, the sensors are very helpful in reducing HbA1c and insulin without degrading the quality of life of patients, they can be used to correct insulin therapy, but must be worn for at least 70% of the time and, in children, require further studies.

The PGLS *(Predictive Low Glucose Suspend)* is currently the most important technology for automatic prevention of hypoglycaemia. Combined with SAP, it is really important in patients with many hypoglycemic episodes, not on target and where it is important to reduce the HbA1c by reducing the hypoglycaemia; it is favourably cost effective.

The artificial pancreas hybrid, already on the US market for about 1 year, will probably soon arrive in Europe. Many studies have been conducted and it has been used by many patients, demonstrating, in a meta-analysis, that it reduces blood glucose by an average of 10 mg/dL, reducing hypoglycaemia and increasing the time in range (TIR).[28] Pancreas islet transplantation is also a reality and it has proved able to cure diabetes, representing the 4a line of treatment of T1D.

Fig. 4. Proposed treatment algorithm for patients with T1D and hypoglycaemia problems



L. Piemonti, Diabetes Research Institute

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FURTHER INFORMATION

Medical Education (CME)

This activity has been approved by Agenas (ref number 142 – 229386) for a total of 6.5 credits.

Educational grant

This programme is made possible thanks to an independent educational grant from Novo Nordisk A/S.

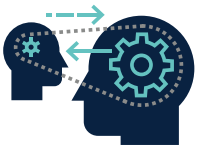
Organiser

This educational activity was planned and independently implemented by Springer Healthcare IME.

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

SATELLITE SYMPOSIUM
at ESPE 2018

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

Saturday 29th September 2018
Athens Megaron Conference Centre, Athens, Greece
With Professor Francesco Chiarelli & Professor Tadej Battelino

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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