

Available tools for primary ketoacidosis prevention at diabetes diagnosis in children and adolescents* “The Parma campaign”

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Abstract. Diabetic Ketoacidosis (DKA) is a leading cause of death and disability in children with type 1 diabetes (T1D) and it is generally related to a long duration of misdiagnosed hyperglycaemia-related symptoms. Shortening this latency period could be a winning preventive strategy. It is intuitively easy to achieve this goal when other members with T1D in a family exist, as well as during the follow-up of the relatives of patients with T1D positive for genetic, immunological or metabolic markers. An incidental blood glucose level over 100 mg/dl found in children without history for T1D has been reported as indicative of a progressive beta-cell dysfunction and so it may be recommended for DKA prevention at diabetes diagnosis. More encouraging results have been obtained with a campaign of information promoted in schools and in paediatricians' offices, centred on the earliest symptom of diabetes (nocturnal enuresis in a dry child) as reported by 89% of parents. During 8 years of this campaign, the cumulative frequency of DKA dropped from 78% to 12.5% and its long effects were still observed several years after it was promoted. The Parma campaign obtained a reduction in DKA incidence at diabetes diagnosis never found before. The key-success of this campaign may be attributed to the communication of a valuable and reliable message easy to understand and follow; information toward a large population through school and paediatric consultation; involvement of family paediatricians and Parents' Association; free access to experienced health providers in diabetes diagnosis. (www.actabiomedica.it)

Key words: Type-1-Diabetes, DKA, prevention, children, adolescents, World Diabetes Day, United Nations

The United Nations (UN) General Assembly unanimously adopted on December 20th, 2006 the Resolution n. 61/225, entitled “World Diabetes Day”, which recognizes the severity of diabetes and encourages the Member States to develop national policies for the prevention, treatment, and care of diabetes. This Resolution is closely linked to the UN Millennium

Development Goals of the UN's targets for 2015, Millennium Goal number 4: to reduce child mortality worldwide. In this scenario, the International Diabetes Federation (IDF) declared 2007 to be the Year of the Child and spread the message that no child should die of diabetes. The World Diabetes Day campaign 2007-2008 aims to reduce child mortality worldwide and to

*The Publisher is proud to host in the current issue the text of the Plenary lecture given by Professor Maurizio Vanelli at the annual meeting of the International Society for Paediatric and Adolescent Diabetes (ISPAD), held in Berlin, Germany, on September 27, 2007. Professor Vanelli is one of the 22 worldwide members of the International IDF Board who prepared the Youth Charter, an important document that supports the United Nations Resolution on diabetes. No topic could be more appropriate for the first UN-observed World Diabetes Day campaign 2007-2008 that the IDF declared to be the Year of the Child.

improve survival and the quality of life of children and adolescents with Typ-1-Diabetes (T1D). The second goal of this campaign is to reduce the global incidence of Diabetic Ketoacidosis (DKA) in children at the time of diagnosis (1).

T1D is still the most prominent form of diabetes in childhood and adolescence. According to the IDF Diabetes Atlas, children aged between 0 and 14 yrs with T1D are estimated to be 440,000 with an annual increase of 3% and with 70,000 newly diagnosed cases every year (2).

T1D at diagnosis continues to be complicated by DKA in a large number of patients. Published incidence rates of DKA range from 15 to 67% (3). The frequency of T1D is associated with the increased risk of children dying from diabetes. Many deaths are due to DKA even in developed countries. Around 80% of deaths in newly diagnosed young patients under the age of 20 in the UK are estimated to be DKA-related (4). Cerebral oedema is recognised to be the most serious complication in DKA occurring in approximately 1% of DKA episodes at diagnosis (5). The “cause” of cerebral oedema is unknown, and the only tool actually available to reduce this complication is the prevention of DKA at diagnosis.

Face to this serious background an effective strategy for DKA prevention must be urgently found. Presently we have only a few evidences of the possibility to prevent or decrease DKA incidence at diabetes onset.

Tools for DKA prevention

According to a recent study, children with a positive family history of T1D present DKA at diagnosis 50% less than those without a family history of T1D (29 vs 60%) (6). High levels of awareness in these families allow parents to perform a prompt blood glucose determination or urine glucose measurement when hyperglycemia-related symptoms appear. In our experience, most diagnoses are directly made by parents at home during an intercurrent illness (76%), a surgical intervention (11%) or accidentally (13%). The widespread reported symptoms are bed-wetting (67%), increased thirst, and nicturia. This information has to be transfer-

red to both the parents with T1D and paediatricians if we want promptly to achieve the goal of DKA prevention in these critical situations.

Further evidences may be found in genetic, immunological and metabolic screening studies in relatives of patients with T1D. Three quarters of the relatives enrolled in the DPT-1 (Diabetes Prevention Trial-1) study in which diabetes developed, were asymptomatic at the time of diagnosis (7). The same study revealed that a rising HbA1c may predict the diagnosis of T1D, thus offering another means to perceive an episode of DKA at onset. Early diagnosis through immunologic and genetic screening of high-risk children has been reported in the EPP-SCIT (European Prediabetes Prevention-Subcutaneous Insulin Trial) in which none of the 14 first-degree relatives in which diabetes appeared, had DKA at onset (Personal communication).

It is unthinkable that these screening studies, originally designed for risk prediction of T1D, could be recommended as a way to avoid DKA at diabetes onset since they have at least three weak points: most of the children with T1D do not have a family history of diabetes and are thus inevitably excluded from the screening; immunological and genetic investigations continue to be too expensive to be enlarged to the general population; these studies exclude family Paediatricians, which should be on the contrary involved in the programmes for the early diagnosis of both T1D and DKA.

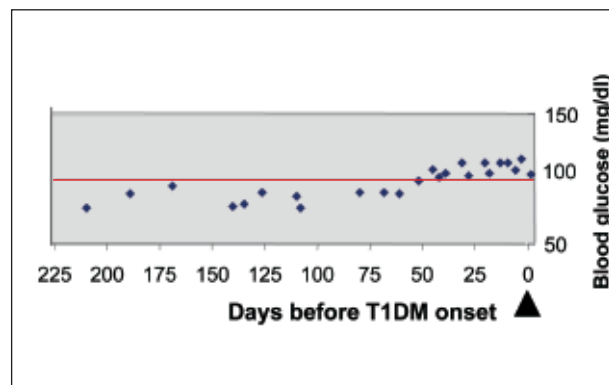


Figure 1. Incidental fasting blood glucose levels found in the history of 22 children before T1D diagnosis

Based on these considerations, other more feasible means should be explored. If we speculate on the signs and symptoms of T1D reported in the weeks before diagnosis, we notice two findings which could be valuable for the early diagnosis of T1D and DKA prevention: incidental elevated glycaemia and unusual bed-wetting in a normally dry child. These findings have a limited effectiveness since they are often misdiagnosed by practitioners and paediatricians.

Many newly diagnosed diabetic children incidentally undergo a fasting blood glucose test a few weeks before diagnosis. In a certain number of these patients blood glucose levels exceed the normal limit of 100 mg/dl. If confirmed, these blood glucose levels could be representative of a latent hyperglycaemia, due to a progressive beta-cell loss (8, 9).

Investigating the history of some T1D patients attending our Unit we found that 22 patients incidentally underwent a fasting blood glucose determination long before becoming diabetic. In 12 of these patients the blood glucose levels were over the normal limit of 100 mg/dl (5.6 mmol/l) 50 days before the diabetes diagnosis (Figure 1). These measurements were misdiagnosed by the paediatricians and diabetes was recognised only when the classic hyperglycaemia-related symptoms appeared. In all of these children the diabetes at onset was complicated by a severe (n. 5/12) or moderate (n. 7/12) DKA.

The challenge to give a prognostic value of a confirmed incidental fasting blood glucose level over 100 mg/dl in children without family history of T1D, obesity, or intercurrent illness, has been considered by the Diabetes Group of ISPED (Italian Society of Paediatric Endocrinology and Diabetology). More than 700 subjects were admitted to the study and tested for genetic, immunological, and specific metabolic markers. Sixteen children (2.1%) resulted positive for two or more autoantibodies and were entrusted to family paediatricians for the follow-up. After a mean 42-month follow-up, paediatricians promptly recorded hyperglycaemia-related symptoms in 11 patients before the development of DKA (9). Despite these results, it is difficult to imagine a campaign for DKA prevention based only on incidental hyperglycaemia since a small percentage of normal children routinely undergo a fasting blood glucose determination du-

ring paediatric practice, and since the prognostic power of a hyperglycaemia accidentally found in asymptomatic children is low (2.1%).

A high index of awareness of early signs of diabetes in children is suitable to decrease the incidence of DKA with new-onset diabetes. In this perspective, we noted that most parents (89%) of newly diagnosed children pointed out unusual bed-wetting in their usually dry children, long before the appearance of classic hyperglycaemia-related symptoms. We addressed our attention to this repetitively reported sign and programmed a strategy to change the course of diabetes at onset. This strategy, commonly known as "Parma campaign" is based on the hypothesis that DKA may be prevented by shortening the period of carbohydrate intolerance that usually precedes T1D diagnosis (10).

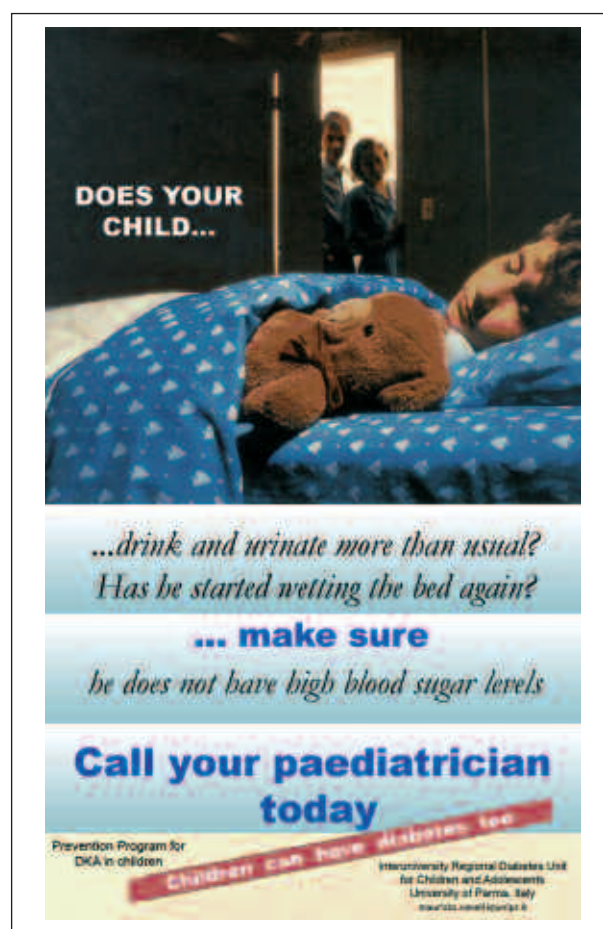


Figure 2. The historical poster used for the Parma campaign from 1991 to 1998

Parma campaign

The campaign was promoted in schools and in paediatricians' offices in the province of Parma, located in Northern Italy, with the principal focus on bed-wetting, the first warning symptom punctually reported by the parents of children with T1D at onset. Information was provided through a poster showing a child sleeping – and potentially wetting the bed – which carried five practical messages (Figure 2): Does your child drink and urinate more than usual? Has he started wetting the bed again? Make sure he does not have high blood sugar levels. Call your paediatrician today. Children can have diabetes too (10).

The poster was displayed in primary and secondary schools and issued to paediatricians working in the province of Parma. Healthcare providers, including doctors, nurses, residents, and social workers with experience in diabetes management explained the aims of our campaign to teaching staff. The teachers were invited to show the poster to parents during routine meetings.

In addition, a card outlining guidelines for the diagnosis of type 1 diabetes was distributed to paediatricians, listing the early symptoms (bed-wetting, excessive thirst) of incipient diabetes, and the World Health Organization criteria for diagnosis. Paediatricians were asked to promptly refer children with the clinical features mentioned above to our diabetes unit. Local paediatricians were instructed on the use of glucose meters in order to perform a prompt capillary blood glucose measurement directly in their offices. In order to facilitate contact with our diabetes unit, a toll-free number was provided by the Parents Association of Children with Diabetes of Parma.

During 8 years of monitoring, the cumulative frequency of DKA in the province of Parma dropped from 78% to 12.5%; after the first 2 years of the campaign, none of the newly diagnosed children with diabetes were admitted to our diabetes unit with severe DKA. In the two control-provinces in which the campaign was not carried out, the incidence of children with type 1 diabetes with severe or moderate DKA was higher (83%), similar to that

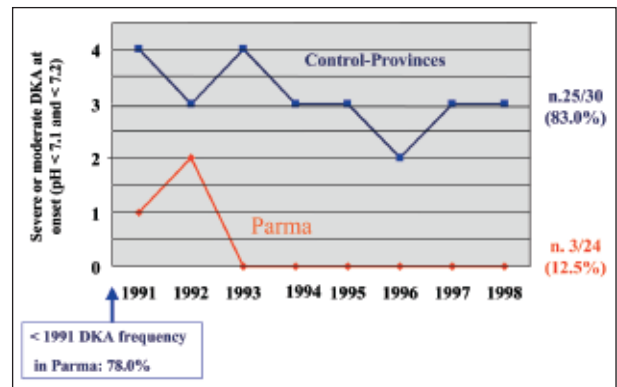


Figure 3. Cumulative frequency of severe and moderate DKA episodes at diagnosis observed in the province of Parma during campaign and in the two control-provinces

observed in the province of Parma before the beginning of the preventive campaign (Figure 3).

The decrease of DKA incidence in children with diabetes in the province of Parma intuitively resulted from the children experiencing a shorter period of metabolic derangement prior to developing overt diabetes. Our starting hypothesis has been demonstrated.

The total cost of the 8-year campaign was 23,470 USD, including the toll-free telephone line, posters, and time spent by healthcare providers in answering the telephone and providing education for teachers. Given the benefits obtained, it is reasonable to consider the campaign as cost-effective or better a cost-less campaign (10).

Eight years have passed since the end of the campaign. In order to evaluate the long-term benefits, we studied the newly diagnosed children with diabetes who were admitted to our unit between January 1999 and December 2006. We found that 81% of the children from the province of Parma did not have severe DKA, compared to 27% of those from the two neighbouring provinces in which no campaign had been carried out. Five unexpected severe episodes of DKA in children from Parma were observed between 2004 and 2006 (Figure 4). This finding, added to the report that almost all posters displayed in the schools had disappeared over the years, indicates that time has weakened the campaign and that it needs to be renewed in order to regain

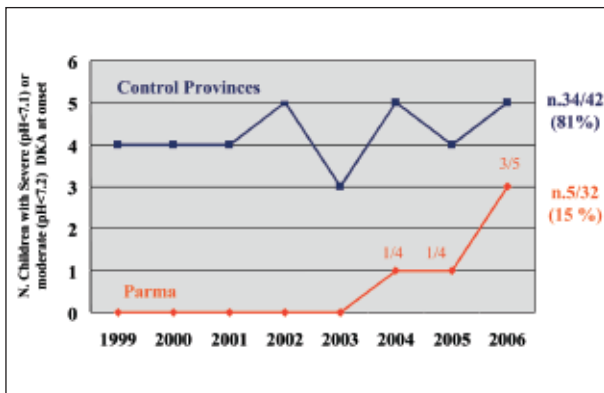


Figure 4. Long-term benefits of the campaign on cumulative frequency of severe and moderate DKA episodes at diagnosis observed in the province of Parma from 1999 to 2006 compared to the control-provinces

its effectiveness (11, 12).

In conclusion, the Parma campaign obtained a reduction in DKA incidence at diabetes diagnosis never found before. The key-success may be attributed to at least four strength points: communication of a valuable and reliable message that is easy to understand and follow ; information towards a large population through school and paediatric consultation ; involvement of family paediatricians and Parents' Association; easy and free access to experienced health providers in diabetes diagnosis; the benefits were achieved at minimal cost and led us to encourage groups in other areas to repeat our experience.

Given the difficulty in obtaining continuous collaboration from schools, alternative sites should be considered when deciding where to display the posters. We recommend public places, such as pharmacies and paediatric departments, which are regularly visited by many people who are attentive to their children's health problems.

According to these findings and thanks to the collaboration of NovoNordisk-Italy, we are ready to promote a new edition of the "Parma campaign" in occasion of the World diabetes day, extended at Country level. During the year dedicated to children with diabetes, 15.000 Italian family paediatricians will receive a new poster edition to display in their offices (Figure 5) and two types of post-cards with a drawing of a child who experienced bed-wetting at

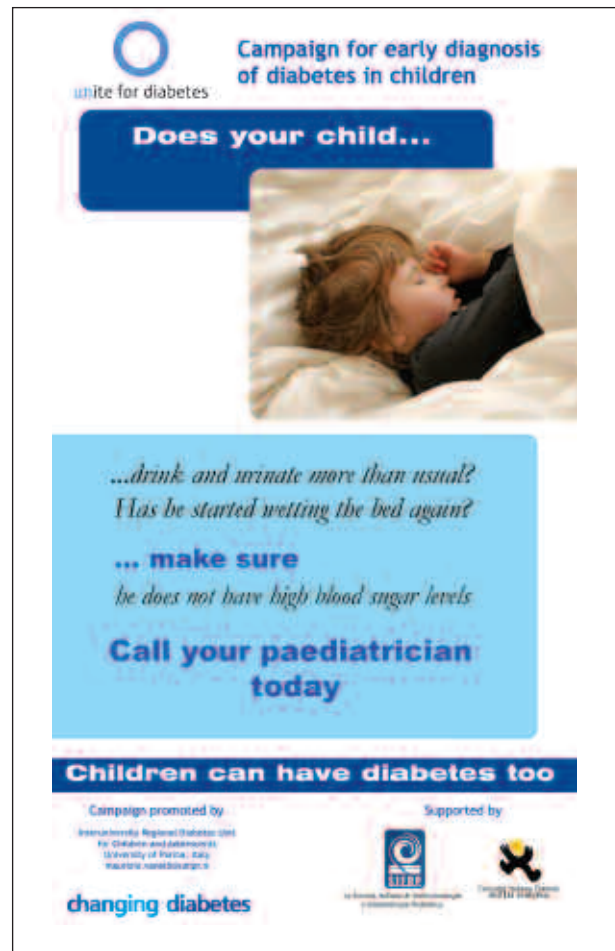


Figure 5. New poster edition for Parma campaign

the time of diabetes onset. The first post-card is for paediatricians to remind them that bed-wetting in an usually dry patient could be an early symptom of incipient diabetes. The second one is retained for the parents consulting a paediatrician's office which can transfer home the same message displayed on the poster (Figure 6). Due to this new public promotion we can virtually contact millions of Italian families.

In the near future the campaign will be extended to schools, pharmacies, and paediatric departments with the collaboration of paediatrician diabetologists working in the eighty regional and province centres which constitute the Italian network for the management of diabetes in children and adolescents.



Figure 6. Post-card for the parents consulting a paediatrician's office

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