

Diabetic ketoacidosis at the onset of disease during a national awareness campaign: a 2-year observational study in children aged 0–18 years

Ivana Rabbone ¹, Giulio Maltoni,² Davide Tinti,¹ Stefano Zucchini,² Valentino Cherubini,³ Riccardo Bonfanti,⁴ Andrea Scaramuzza ⁵,⁵ On behalf of the Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology (ISPED)

¹Pediatric, Città della Salute e della Scienza di Torino, Turin, Italy

²Pediatric Department, S Orsola Malpighi Hospital, University of Bologna, Bologna, Italy

³Regional Center for Diabetes in Children and Adolescents, Department of Woman and Child Health, AOU Salesi Hospital, Ancona, Italy

⁴Pediatrics, Ospedale San Raffaele, Milano, Italy

⁵Pediatrics, Azienda Socio Sanitaria Territoriale di Cremona, Cremona, Italy

Correspondence to

Dr Andrea Scaramuzza, Pediatrics, Azienda Socio Sanitaria Territoriale di Cremona, Cremona 26100, Italy; a.scaramuzza@gmail.com

Accepted 21 September 2019

ABSTRACT

Objective After a previous survey on the incidence of diabetic ketoacidosis (DKA) at onset of type 1 diabetes in children in 2013–2014 in Italy, we aimed to verify a possible decline in the incidence of DKA at onset during a national prevention campaign.

Design Prospective observational study.

Setting Multicentre study throughout Italy.

Intervention National awareness campaign started in November 2015 and held until December 2017.

Patients During 2016 and 2017 we collected data on all patients aged 0–18 years with new-onset diabetes.

Main outcome measures DKA (pH <7.30), severe DKA (pH <7.1), DKA in children below 6 years and DKA treatment according to the Italian Society for Pediatric Endocrinology and Diabetology (ISPED) protocol were evaluated.

Results Records (n=2361) of children with newly diagnosed type 1 diabetes were collected from 58 out of 68 (85.3%) centres of the original survey participants and 100% of the previously surveyed tertiary centres. Overall, DKA was observed in 1124 patients, with an increased rate when compared with the previous survey (47.6% vs 38.5%, p=0.002), and severe DKA in 15.3%. In children below 6 years, DKA was observed in 323 out of 617 (52.5%) and severe DKA in 16.7%; in this age group, occurrence of DKA reduced by 21.3% (p=0.009). DKA treatment according to the ISPED guidelines was adopted in 95% of the centres, with a 27% improvement (p=0.025).

Conclusions During a 2-year awareness campaign, DKA at onset of diabetes in children and adolescents 0–18 years is still common and increased when compared with the 2013–2014 survey.

INTRODUCTION

In calendar years 2012 and 2013, paediatric endocrinologists belonging to the Italian Society for Pediatric Endocrinology and Diabetology (ISPED) conducted a multicentre retrospective survey,¹ the aims of which were (1) to evaluate the incidence of diabetic ketoacidosis (DKA) at onset of type 1 diabetes in children and adolescents in Italy, and (2) to determine utilisation of the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines about DKA management in various centres. In more than 2400 new cases of type 1

What is already known on this topic?

- ▶ Diabetic ketoacidosis (DKA) is a threatening event in the course of diabetes either at onset or during follow-up.
- ▶ DKA incidence does not seem to decrease despite the awareness campaign, at least at a national level.
- ▶ Awareness campaigns displayed in a smaller context (ie, Emilia Romagna region in the Parma campaign, or Newcastle area in Australia) seem to be more effective.

What this study adds?

- ▶ DKA incidence has increased in the calendar years 2016–2017 compared with 2013–2014, either as overall DKA incidence or as severe DKA incidence, in Italy.
- ▶ Compared with the previous survey, a decreased incidence rate in DKA has been observed in preschool children (under 6 years of age).
- ▶ After their publication, 95% of the Italian centres used the DKA recommendation of the Italian Society for Pediatric Endocrinology and Diabetology.

diabetes, the overall incidence of DKA was 38.5%, and 10.3% of patients presented in severe DKA (pH <7.1). In preschool-aged children (aged 6 years or younger), DKA incidence reached more than 70% and was severe in 16.6% of cases.¹ Only 68% of centres reported adoption of the ISPAD guidelines to manage DKA, and there was great variation in the approach to management.¹ These data were consistent with a comprehensive study of DKA incidence during a 10-year follow-up in Italy by Cherubini *et al*,² and with studies published in the same period in other European^{3–5} and Extra European countries.^{6,7}

Despite several efforts to reduce the occurrence of DKA at onset of type 1 diabetes, there continues to be an unacceptably high burden of DKA, with an incidence rate often more than 30%.

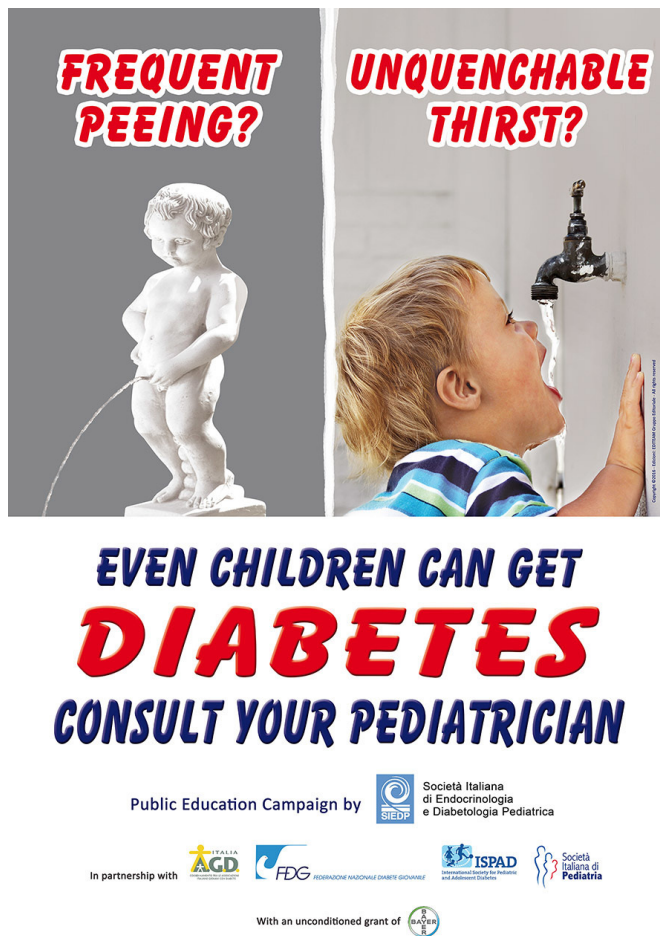


Figure 1 Advertising poster of the Italian campaign in English. This poster is also available in Italian, Arabic, Romanian and Chinese.

Inspired by the successful Parma campaign, which reduced DKA incidence at onset of type 1 diabetes⁸ (even if the positive effect tended to disappear after some time⁹), in 2015 we decided to launch a nationwide awareness campaign intended to prevent DKA at diabetes onset and to pursue the campaign for 2 years. In the mean time, the Diabetes Study Group of the ISPED published its recommendations for DKA treatment¹⁰ partly based on the ISPAD guidelines,¹¹ with some differences,¹² with the aim of standardising the management of DKA in all Italian paediatric diabetes centres.

The primary aim of the present survey was to prospectively evaluate the number of new cases of type 1 diabetes below the age of 19 during the awareness campaign (figure 1) throughout the calendar years 2016 and 2017. The secondary aim was to determine how many Italian centres reported to adhere to the Italian recommendations for DKA treatment.¹⁰

METHODS

A national publicity campaign to increase awareness about DKA has been launched in Italy in November 2015 and is still ongoing, and therefore continued alongside the period of data collection. In Italy, quite all children below the age of 6 years and most of the older ones (8–14 years of age) are under the care of family paediatricians. For this reason the campaign was aimed to family paediatricians, and each of them received an advertising poster (figure 1) to exhibit in their ambulatory setting. Moreover, they received a monthly newsletter via email, highlighting various topics related to DKA. The same advertising poster was

sent to many schools, asking the principal to exhibit it, as well as to families, who receive bimonthly by mail a magazine (*Conoscere per Crescere*, a magazine about growth issues) that features various aspects of paediatrics. In total the advertising poster and the newsletters were sent to 10 000 family paediatricians, while the advertising poster was sent to 250 elementary, junior high or high schools.

The awareness campaign was also launched on ISPED's social media (ie, Facebook and Instagram) and was endorsed by two famous Italian comedians (Ale e Franz; official website: <http://www.alefranz.com/>), who played a short commercial to advertise Italian awareness of DKA campaign and was shown on many national and regional television channels.

After 31 December 2017, all 68 centres that participated in our first survey¹ were invited to complete a survey to collect data and investigate DKA epidemiology and management in patients who presented with new-onset type 1 diabetes during the calendar years 2016 and 2017. The survey questions were identical to those included in the previous survey.¹ To facilitate data collection, the survey was web-based and data collection was centralised at the Turin centre. Each centre was asked to review all records of patients under 19 years of age who had diabetes onset between 1 January 2016 and 31 December 2017.

The following information was requested from each patient: date of birth, date of diabetes onset, pH value at diabetes onset (to evaluate DKA severity), if a published DKA treatment protocol was used (eg, ISPED protocol for DKA¹⁰ or other) and any treatment complication (eg, cerebral oedema).

In the final analysis the following data were analysed: number of patients 0–18 years of age with diabetes onset during the observation period, number of patients <6 years of age, number of patients with DKA (either as a total number or only patients <6 years of age), number of patients with severe DKA (either as a total number or only patients <6 years of age), number of patients who developed cerebral oedema, and number of centres following any DKA protocol and which one.

DKA was defined according to the ISPAD criteria¹¹ (eg, blood glucose >11 mmol/L (\approx 200 mg/dL); venous pH <7.3 or bicarbonate <15 mmol/L; ketonaemia and ketonuria). The severity of DKA was categorised according to the degree of acidosis: (1) mild: venous pH <7.3 or bicarbonate <15 mmol/L; (2) moderate: pH <7.2 or bicarbonate <10 mmol/L; and (3) severe: pH <7.1 or bicarbonate <5 mmol/L.¹¹

Data for the calendar years 2016 and 2017 were pooled for analysis, and we used the χ^2 test to evaluate possible statistical differences between groups; statistical significance was determined to be $p < 0.05$.

RESULTS

Among the 68 centres belonging to the ISPED that participated in the first survey,¹ 58 (85.3%) completed the web-based survey and returned complete data records of patients with newly diagnosed diabetes. One hundred per cent of the tertiary referral centres ($n=39$) of the ISPED were included among the 58 centres that responded.

The results of the current survey compared with those of the previous one¹ are shown in table 1.

In 2016–2017, a total of 2361 children 0–18 years of age were diagnosed with type 1 diabetes in the 58 respondent centres, and their records were evaluated and reviewed for the present report.

DKA was observed in 1123 out of 2361 (47.6%) patients, which is a significant increase in DKA incidence compared with

Table 1 Diabetic ketoacidosis incidence in the paediatric population (0–18 years) in the calendar years 2016 and 2017 in Italy, compared with the previous survey in calendar years 2012 and 2013¹

	2012–2013 survey	2016–2017 survey	P value
Patients with type 1 diabetes onset (n)	2453	2361	–
Preschool patients with type 1 diabetes onset, n (%)	618 (26.6)	617 (26.1)	–
Patients with DKA at onset, n (%)	945 (38.5)	1124 (47.6)	0.002
Preschool-aged patients with DKA at onset, n (%)	445 (73.8)	323 (52.5)	0.009
Patients with severe DKA at onset, n (%)	97 (10.3)	172 (15.3)	0.008
Preschool-aged patients with severe DKA at onset, n (%)	103 (16.6)	70 (21.7)	0.008

DKA, diabetic ketoacidosis.

the 2012–2013 survey¹ (47.6% vs 38.5%, $p=0.002$). Similarly, the rate of severe DKA was significantly increased (table 1).

With an equal number of preschool-aged children in the two surveys ($n=617$, 26.1% in 2016–2017 vs $n=650$, 26.7% in 2012–2013), the incidence of DKA significantly decreased in preschool-aged children in 2016–2017 compared with 2012–2013 (52.5% vs 73.8%, $p=0.009$) (table 1); however, the rate of severe DKA both in preschool-aged children and in the entire cohort increased significantly (table 1).

Cerebral oedema was observed in 4 out of 1123 patients with DKA in the current cohort (0.35% vs 0.53% in 2012–2013, $p=0.548$). Seven cases of mild DKA occurred in adolescents who subsequently were diagnosed with type 2 diabetes at disease onset.

Among the 58 respondent centres, 95% reported following the ISPED DKA treatment recommendations.¹⁰

DISCUSSION

The present survey provides a comprehensive depiction of DKA epidemiology and management in 58 out of 68 centres that provided data about newly diagnosed children 0–18 years old with type 1 diabetes in Italy during the calendar years 2016 and 2017, during an awareness campaign, from November 2015 until the end of 2017. The data collected are considered to represent DKA at the national level because information was obtained from 100% of the tertiary-level centres that participated in the previous survey ($n=39$),¹ which provided coverage of approximately 90% of paediatric diabetes in Italy.

The DKA awareness campaign was directed to family paediatricians throughout Italy. In Italy, since 1978, each child 0–14 years of age has been assigned to a family paediatrician who is responsible for his/her health and disease management. Family paediatricians received by mail one or more advertising posters (figure 1) to exhibit in their ambulatory setting.

Unfortunately, the reach of the campaign has not been measured and only partial figures are available. We sent 10 000 posters but we have no way to verify if all of them have been displayed in the ambulatory setting, as well as how many schools displayed the poster.

An earlier prevention campaign⁸ succeeded in decreasing the occurrence of DKA in the Emilia Romagna region but not throughout Italy. We thought that an extra effort to reduce the occurrence of DKA in new-onset diabetes throughout Italy was needed. It is disappointing that the present survey shows the campaign coincided with an increase in the incidence of DKA in patients with new-onset diabetes. It is difficult to explain the

reason for the higher incidence in 2016–2017 compared with 2012–2013. However, the SWEET consortium has presented similar data at the last annual conference of the ISPAD.¹³

Even if the observational study design does not allow for a definitive conclusion, it is interesting to note that the awareness of DKA campaign was associated with a significant 30% decrease in the incidence of DKA in preschool-aged children. In this respect, family paediatricians, the main target of the awareness campaign, might have played an important role in the early identification of new-onset diabetes in young children.

A previous national awareness campaign in Austria was not able to show a decrease in DKA incidence.¹⁴ The authors described a DKA incidence of 37.2% for all new-onset diabetes in the period 1989–2011, and no difference before and after a prevention campaign that was similar to the Parma campaign.¹⁴ By contrast, Vanelli *et al*⁸ showed a decrease in DKA incidence from 78% to 12%, highlighting the fact that a similar prevention campaign might work better when applied to a small area (the Emilia Romagna region) instead of a national area (eg, Italy and Austria). Similarly, in a small area (Newcastle area of New South Wales, Australia), Bruce King and colleagues¹⁵ reported a decrease in DKA by 64%.

It is also disappointing that the awareness of DKA campaign coincided with a higher incidence of severe DKA when compared with 2012–2013 both in the entire cohort and in preschool-aged children. The reason for this increase is unknown. DKA continues to be a threat to all children and adolescents with type 1 diabetes onset despite the campaign to prevent it. The length of the campaign (2 years) may be too short to obtain consistent results. The Austrian campaign took 20 years to attain a 13% decrease in the DKA incidence at diabetes onset in paediatric age.¹⁴ Recent data from the USA showed a steadily increasing incidence of DKA in both children and adults, but associated with a decrease in DKA-associated mortality.¹⁶ Moreover, it is interesting to note that a recent systematic review of publicity interventions to increase awareness among healthcare professionals and the public to promote earlier diagnosis of type 1 diabetes in children and young people does not reach a definitive conclusion on the effectiveness of the interventions reported.¹⁷

The decrease in DKA incidence only in preschool-aged children and not in the entire cohort could also be explained by the ongoing shortage of family paediatricians observed in Italy in the past years, due to a large number of paediatricians retiring in the last 5 years and not being replaced by younger paediatricians. The lower number of family paediatricians is the reason why many families when their children are older than 6 years of age move to family physicians (ie, general practitioners), who were not the target of the awareness campaign. It is likely that general practitioners who care for some older children and adolescents may not have been reached by the campaign.

However, despite the increased number of patients with severe DKA, a slight, non-significant, decrease in the rate of cerebral oedema was observed during 2016–2017. We cannot conclude that this improvement could be due to a higher percentage of recommendation implementation.^{10,11} Certainly, the release of the ISPED recommendations for the management of DKA in 2015¹⁰ enabled a standardisation of the procedures for the management and treatment of DKA in the different Italian centres. While in the previous report only 68% of the centres claimed to follow a treatment protocol based on the ISPAD guidelines, nearly all the centres responding to the present survey reported using the ISPED/ISPAD recommendations.

As a limitation of this study, we would like to note that despite our aim of evaluating whether the campaign was effective in

decreasing DKA incidence, it was not possible to determine the effectiveness using our study design, as there was no control group or experimental design, and changes over time since the last study may have been caused by other changes unrelated to the campaign. Also, the data were collected while the campaign was ongoing, so there was no way of knowing whether the decrease would be sustained following the end of the campaign. We aim to collect data for the next calendar year to sort this out.

In conclusion the findings of this second nationwide survey in the calendar years 2016 and 2017 about the incidence of DKA in children and adolescents at the onset of type 1 diabetes show that DKA is still common at diabetes onset in children and adolescents. A continuous reinforcement of the awareness of DKA prevention campaign is needed and should probably be implemented. New strategies of communication should probably be promoted and supported by scientific societies and national health systems, targeting family paediatricians and general practitioners, as well as the whole population, via radio/television/social media advertising. The Diabetes Study Group of the ISPED is currently working to implement a nationwide awareness DKA prevention campaign.

Twitter Andrea Scaramuzza @andreathedoc

Collaborators Collaborators of the Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology (ISPED). The following people were actively involved in the collection of data and have to be considered as collaborators of the paper: Riccardo Lera (Alessandria); Valentino Cherubini (Ancona); Adriana Bobbio (Aosta); Elvira Piccinno (Bari); Stefano Zucchini, Giulio Maltoni (Bologna); Petra Reinstadler (Bolzano); Barbara Felappi, Elena Prandi (Brescia); Francesco Gallo (Brindisi); Anna Paola Frongia, Carlo Ripoli (Cagliari); Donatella Lo Presti, Letizia Tomaselli (Catania); Giuliana Cardinale (Casarano); Filomena Andreina Stamatii (Castrovillari); Felice Citriniti (Catanzaro); Tosca Suprani, Vanna Graziani (Cesena, Ravenna); Fiorella De Berardinis (Cetraro); Maria Zampolli (Como); Rosaria De Marco (Cosenza); Andrea Scaramuzza, Claudio Cavalli (Cremona); Nicola Lazzaro (Crotone); Valeria De Donno (Cuneo); Sonia Toni, Barbara Piccini, Lorenzo Lenzi (Florence); Benedetta Mainetti (Forlì); Maria Susanna Coccioli (Francavilla Fontana); Giuseppe d'Annunzio, Nicola Minuto (Genoa); Monica Aloe (Lamezia Terme); Sonia Lucchesi (Livorno); Dante Cirillo (Magenta); Silvia Sordelli (Mantova); Maurizio Delvecchio (Matera); Fortunato Lombardo, Giusy Salzano (Messina); Riccardo Bonfanti, Franco Meschi (Milano); Lorenzo Iughetti, Barbara Predieri (Modena); Adriana Franzese, Enza Mozzillo, Dario Iafusco (Naples); Francesco Cadario, Silvia Savastio (Novara); G Piredda (Olbia); Francesca Cardella (Palermo); Brunella Iovane (Parma); Valeria Calcaterra (Pavia); Maria Giulia Berlioli (Perugia); Martina Biagioni (Pesaro); Emili Randazzo (Pisa); Ippolita Patrizia Patera, Riccardo Schiaffini (Roma); Irene Rutigliano (San Giovanni Rotondo); Anna Lasagni (Reggio Emilia); Silvia Innaurato (Rovigo); Alberto Gaiero, Graziella Fichera (Savona); Ivana Rabbone, Davide Tinti, Michela Trada (Turin); Lucia Guerraggio (Tradate); Vittoria Cauvin, Roberto Franceschi (Trento); Gianluca Tornese (Trieste); Alessandro Salvatoni (Varese); Marco Marigliano, Alberto Sabbion, Claudio Maffei (Verona); Claudia Arnaldi (Viterbo).

Contributors IR, GM and SZ were responsible for the study design. All authors, as well as each of the person listed in the Collaborators section, were responsible for the conduct of the study and data collection. IR, DT, AS, VC and RB ran the data analysis and interpreted the data. IR and AS wrote the manuscript, and all authors read the paper and contributed to the discussion.

Funding We would like to thank Ascensia Italia for a non-conditional grant that supported the printing of the advertising posters.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs

Ivana Rabbone <http://orcid.org/0000-0003-4173-146X>

Andrea Scaramuzza <http://orcid.org/0000-0002-1518-8515>

REFERENCES

- Zucchini S, Scaramuzza AE, Bonfanti R, *et al.* A multicenter retrospective survey regarding diabetic ketoacidosis management in Italian children with type 1 diabetes. *J Diabetes Res* 2016;2016:5719470.
- Cherubini V, Skrami E, Ferrito L, *et al.* High frequency of diabetic ketoacidosis at diagnosis of type 1 diabetes in Italian children: a nationwide longitudinal study, 2004-2013. *Sci Rep* 2016;6:38844.
- Vukovic R, Jescic MD, Vorgucin I, *et al.* First report on the nationwide incidence of type 1 diabetes and ketoacidosis at onset in children in Serbia: a multicenter study. *Eur J Pediatr* 2018;177:1155-62.
- Große J, Hornstein H, Manuwald U, *et al.* Incidence of diabetic ketoacidosis of new-onset type 1 diabetes in children and adolescents in different countries correlates with human development index (HDI): an updated systematic review, meta-analysis, and meta-regression. *Horm Metab Res* 2018;50:209-22.
- Eyal O, Oren A, Almasi-Wolker D, *et al.* Ketoacidosis in newly diagnosed type 1 diabetes in children and adolescents in Israel: prevalence and risk factors. *Isr Med Assoc J* 2018;20:100-3.
- Patwardhan R, Gorton S, Vangaveti VN, *et al.* Diabetic ketoacidosis incidence in children at first presentation of type 1 diabetes at an Australian regional Hospital: the effect of health professional education. *Pediatr Diabetes* 2018;19:993-9.
- Horvat CM, Ismail HM, Au AK, *et al.* Presenting predictors and temporal trends of treatment-related outcomes in diabetic ketoacidosis. *Pediatr Diabetes* 2018;19:985-92.
- Vanelli M, Chiari G, Ghizzoni L, *et al.* Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care* 1999;22:7-9.
- Vanelli M, Chiari G, Lacava S, *et al.* Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care* 2007;30:e12.
- Rabbone I, Bonfanti R, Buono P, *et al.* Raccomandazioni per La gestione DELLA chetoacidosi diabetica in et pediatrica. *Acta Biomedica* 2015;86:5-26.
- Wolfsdorf JI, Allgrove J, Craig ME, *et al.* Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2014;15:154-79.
- Rabbone I, Wolfsdorf J, Ragnar H. Diabetic ketoacidosis management in children and adolescents. ISPAD Versus ISPED: similarities and differences. In: Scaramuzza AE, de Beaufort C, Hanas R, eds. *Research into childhood-onset diabetes: from study design to improved management*. Springer, 2017: 11-19.
- Cherubini V, Akesson K, Birkebaek NH, *et al.* DKA at onset of pediatric type 1 diabetes across the world: results from a joint international project. *Pediatr Diabetes* 2018;19(Suppl 26):28-9. (abstract).
- Fritsch M, Schober E, Rami-Merhar B, *et al.* Diabetic ketoacidosis at diagnosis in Austrian children: a population-based analysis, 1989-2011. *J Pediatr* 2013;163:1484-8.
- King BR, Howard NJ, Verge CF, *et al.* A diabetes awareness campaign prevents diabetic ketoacidosis in children at their initial presentation with type 1 diabetes. *Pediatr Diabetes* 2012;13:647-51.
- Desai D, Mehta D, Mathias P, *et al.* Health care utilization and burden of diabetic ketoacidosis in the U.S. over the past decade: a nationwide analysis. *Diabetes Care* 2018;41:1631-8.
- Deylami R, Townson J, Mann M, *et al.* Systematic review of publicity interventions to increase awareness amongst healthcare professionals and the public to promote earlier diagnosis of type 1 diabetes in children and young people. *Pediatr Diabetes* 2018;19:566-73.