Achieving the Management Goals of Type 1 Diabetes in Children and Adolescents: Is It Feasible?

Ori Eyal MD, Asaf Oren MD and Naomi Weintroub MD MPH

Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: type 1 diabetes mellitus (T1DM), diabetic ketoacidosis (DKA), glycemic control, adolescents

IMAJ 2013; 15: 363–365

The incidence of type 1 diabetes mellitus has been increasing steadily in the western world [1], including Israel [2]. The rising incidence should heighten our level of awareness for diagnosing and treating T1DM, but data from the EURODIAB study [3] show that the standard mortality ratio for children with diabetes compared to healthy children has remained constant at around 2 over the last 15 years. Since the leading cause of mortality in children with T1DM is diabetic ketoacidosis [3], it follows that lowering the DKA rate should decrease mortality. There is wide geographic variation in the frequency of DKA, with the rate of DKA in newly diagnosed type 1 diabetics being inversely correlated with its incidence [4]. It would therefore be reasonable to expect a decrease in the DKA rate with an increase in incidence. This turns out not to be the case: the DKA rate has remained fairly constant over the last 20 years while the type 1 diabetes rate has increased [2]. DKA at presentation of T1DM is more common in young (0–4 years old) children of parents with low education level and low socioeconomic status [5]. The findings of Hilmi et al., published in this issue of *IMAJ* [6], are in agreement with these data. Those authors reported that the rate of DKA at presentation was significantly higher among the Bedouin population in the Negev compared to the Jewish population in the same area. The incidence of T1DM in the Bedouin population in Israel is about half that of the Israeli Jewish population [6]. The lower incidence of T1DM and the lower socioeconomic status of the Bedouin population might partially explain this difference.

DKA is the leading cause of morbidity and mortality in children with T1DM [3] and its prevention should be a major goal in treating diabetic youngsters. An increased awareness of the symptoms of diabetes in the general population among primary care physicians may allow for earlier diagnosis, thus preventing DKA. Vanelli and team from southern Italy [7] reported that an increase in the level of awareness due to intensive education at schools, and among medical teams and the general public reduced the rate of DKA at first presentation of T1DM from 78% to an extraordinary 12.5% over a period of only 6 years! Prompt implementation of similar programs in Israel, especially among high risk populations such as the Bedouin community, is therefore urgently needed.

The clinical course of T1DM, including its treatment, metabolic outcomes, and long-term complications, has changed dramatically throughout the past 30 years [8]. Treatment innovations, including multiple daily injection regimens, continuous subcutaneous insulin infusion with external pumps [9], new rapid and long-acting insulin analogues with more physiological pharmacokinetic characteristics [10], widespread self-monitoring of blood glucose, and improved treatment of comorbidities (e.g., hypertension and dyslipidemia) have all contributed to changes in the management of T1DM. Despite great advances in diabetes care, T1DM is still associated with considerable premature mortality caused by both acute and chronic complications of diabetes [11].

There is alarming evidence that the pathogenesis of complications begins soon after diagnosis during childhood and accelerates during puberty [12]. Thus, adolescence may be a critical period for determining the lifetime risk of complications in childhood-onset T1DM.

The goals of T1DM treatment have changed since the large-scale randomized controlled Diabetes Control and Complications Trial (DCCT) and its long-term observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study [8], which demonstrated reduced long-term complications with intensive diabetes therapy and better glycemic control. The limiting factor for achieving near-normal glycemic control was the markedly increased rate of severe hypoglycemic episodes in the intensively treated group compared to the conventionally treated group, which was even more frequent in adolescents despite worse HbA1c levels as compared to young adults. In addition, many youths and families of children with T1DM are not able to cope with the day-to-day "burden" of intensive diabetic therapy. Interestingly, previous pediatric studies have shown that the motivation of the caregivers and the patients has a larger impact on diabetic control than the mode of insulin delivery [13].

Achieving an optimal level of glycemic control continues to be challenging. Indeed, the mean HbA1C of the patients described by Hilmi et al. [6] in both the

T1DM = type 1 diabetes mellitus
DKA = diabetic ketoacidosis

Jewish and Bedouin study groups was well above the target glycemic control recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD) [14]). There is a wide variability in glycemic control of children and adolescents among countries and among different centers in the same country. There is also a strong correlation between glycemic targets and metabolic control and outcome [15], suggesting that the dedication of the caregivers, the available resources, and setting of therapeutic targets significantly impacts glycemic control.

Hilmi and co-authors [6] found that glycemic control was worse and that the use of advanced technology was lower in the Bedouin group compared to the Jewish group. Others have suggested that racial and/or ethnic minorities as well as individuals of low socioeconomic status have less access to preventive and daily medical treatment [16] and therefore might experience more long-term complications and increased mortality. It is well recognized that a complex range of self-care behaviors is required to manage diabetes, among them dietary restrictions, regular exercise, adherence to the treatment regimen, self-monitoring of blood glucose, and maintaining glycemic control during acute illness. Language barriers can also hamper education and compliance, and culturally tailored interventions can be effective in reducing disparities in diabetes care and outcome. Kalter-Leibovici et al. [17] recently showed that a culturally sensitive intensive lifestyle intervention was effective in improving metabolic syndrome components among obese Arab women in Israel. Interventions focusing on interpersonal connections were reportedly more influential than technical and computer-based interactions [16].

New and advanced technology in the management of diabetes, such as insulin pumps [9,13] and continuous glucose monitoring [18,19], have emerged over the past few years, but their impact was mainly on quality of life and not on glycemic control, especially among children and adolescents [13,18]. Although insulin pumps enable physiological delivery of insulin, and glucose sensors provide continuous glucose patterns, it is still difficult to achieve good glycemic control in children and adolescents because those processes comprise only one arm of diabetes care. Furthermore, these modalities must be implemented correctly in order to improve glycemic control, which limits their use to competent and highly motivated patient groups [19]. Finally, diet and physical activity are also critically essential factors, and they are problematic in this age group.

Of note, the intensified therapy in the DCCT not only pertained to the mode of insulin delivery and the frequency of self-monitoring of blood glucose, but also to the frequency of clinical visits and communications between the patients and the multi-disciplinary team. Intensive therapy is costly, but it leads to fewer complications and improves life expectancy, and so the increased cost of therapy is offset by cost savings due to reduced expenditures for complications [20].

The report by Hilmi et al. [6] is therefore extremely important in that it reminds us that the day-to-day coping with diabetes, despite implementing the DCCT's intensive therapy methods, is still far from achieving our goals of glycemic control, suggesting that new ways of coping are needed. These data clearly indicate the importance of making resources available to recruit dedicated professional teams that can provide modern-day diabetes care. Special teams from the Arab and Bedouin populations should be trained to better manage patients from these communities.

Corresponding author
Dr. N. Weintrob
Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
email: naomiw@tlvmc.gov.il

DCCT = Diabetes Control and Complications Trial

References

1. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 2009; 373: 2027-33.
2. Koton S; Israel IDDM Register Study Group – IIRSG. Incidence of type 1 diabetes mellitus in the 0- to 17-yr-old Israel population, 1997-2003. *Pediatr Diabetes* 2007; 8: 60-6.
3. Patterson CC, Dahlquist G, Harjutsalo V, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 2007; 50: 2439-42.
4. Lévy-Marchal C, Patterson CC, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. *Diabetologia* 2001; 44 (Suppl 3): B75-80.
5. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in Ontario children. *Diabetes Care* 2002; 25: 1591-6.
6. Hilmi A, Pasternak Y, Friger M, Loewenthal N, Haim A, Hershkovitz E. Ethnic differences in glycemic control and diabetic ketoacidosis rate among children with diabetes mellitus type 1 in the Negev area. *IMAJ* 2013; 15: 335-8.
7. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. 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.
8. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). *Arch Intern Med* 2009; 169: 1307-16.
9. Weintrob N, Shalitin S, Phillip M. Why pump? Continuous subcutaneous insulin infusion for children and adolescents with type 1 diabetes. *IMAJ* 2004; 6: 271-5.
10. Murphy NP, Keane SM, Ong KK, et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 2003; 26: 799-804.
11. Harjutsalo V, Forsblom C, Groop PH. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *BMJ* 2011; 343: d5364.
12. Kostraba JN, Dorman JS, Orchard TJ, et al. Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 1989; 12: 686-93.
13. Weintrob N, Benzaquen H, Shalitin S, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in children with type 1 diabetes. *Pediatrics* 2003; 112: 559-64.
14. Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P, Klingensmith GJ. ISPAD clinical practice consensus guidelines 2009 compendium assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatric Diabetes* 2009; 10 (Suppl 12): 71-81.

15. Swift PG, Skinner TC, de Beaufort C, et al. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere Childhood Diabetes Study Group Centre Differences Study 2005. *Pediatr Diabetes* 2010; 11: 271-8.

16. Golden SH, Brown A, Cauley JA. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors – an endocrine society scientific statement. *J Clin Endocrinol Metab* 2012; 97: E1579-639.

17. Kalter-Leibovici O, Younis-Zeidan N, Atama A, et al. Lifestyle intervention in obese Arab women: a randomized controlled trial. *Arch Intern Med* 2010; 170: 970-6.

18. Weintrob N, Schechter A, Benzaquen H, et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes treated by multiple daily injections of regular and NPH insulin or continuous subcutaneous insulin infusion with Lispro. *Arch Pediatr Adolesc Med* 2004; 158: 677-84.

19. Hirsch IB. Realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. *J Clin Endocrinol Metab* 2009; 94: 2232-8.

20. Palmer AJ, Weiss C, Sendi PP, Neeser K. The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective. *Diabetologia* 2000; 43: 13-26.

Capsule

Macrophage replenishment in tumors by the spleen

Solid tumors contain not only malignant cells but also a wide array of host-derived cells that can have dramatic effects on tumor behavior. These include macrophages, immune cells that enhance tumor progression in part by promoting inflammation and whose presence in tumors correlates with reduced patient survival times. Macrophages must be continually replenished as the tumor grows, but little is known about this replenishment process. Studying mice bearing lung cancers produced by activation of the RAS oncogene, Cortez-Retamozo et al. found that tumor-associated macrophages are supplied by the spleen, through amplification of hematopoietic stem cells and macrophage progenitor cells. This cell amplification process was stimulated by angiotensin II, a peptide hormone better known for its role in the renin-angiotensin system, which regulates blood pressure. Notably, mice treated with the blood pressure medication enalapril, which inhibits angiotensin II production, had fewer tumor-associated macrophages and fewer lung tumor nodules than control mice. Whether these results can be extrapolated to human lung cancer remains to be determined.

Immunity 2013; 38: 296

Eitan Israeli

Capsule

A role for IFNε

Type I interferons (IFNs) are critical cytokines involved in host defense against pathogens, particularly viruses. IFNε is an IFN-like gene encoded within the type I IFN locus in mice and humans whose function has not been characterized. Fung and co-authors created mice with a genetic deletion in *Ifnε* and found that, like other type I IFNs, IFNε signals through the IFNα receptors 1 and 2. However, unlike these other cytokines, which are primarily expressed by immune cells and are induced upon immune cell triggering, IFNε was expressed exclusively by epithelial cells of the female reproductive tract in both mice and humans and its expression was hormonally regulated. IFNε-deficient mice were more susceptible to infection with herpes simplex virus 2 and *Chlamydia muridarum*, two common sexually transmitted pathogens.

Science 2013; 339: 108

Eitan Israeli

Capsule

Immunomodulation in adult epilepsy: the role of IVIG

Much of the research on intravenous immunoglobulin (IVIG) use in epilepsy has focused on childhood epilepsies and the results have been inconclusive. With the accumulation of evidence for inflammation in epilepsy and epileptogenesis, IVIG might have a role to play in adult epilepsy. In a literature review Sharp and Javidan focus on the purported mechanisms of IVIG, the link between inflammation and the various causes of adult epilepsy, and the different steps of epileptogenesis at which inflammation might play a role. They also review the current clinical evidence supporting IVIG as a treatment for epilepsy in the adult population. Though there is interesting theoretical potential for treatment of refractory epilepsy in adults with IVIG, there is insufficient evidence to support its standard use. The question remains if IVIG should still be considered as an end-of-the-line option for patients with epilepsy poorly responsive to all other treatments.

Can J Neurol Sci 2012; 39 (5): 584

Elias Toubi