

TYPE 1 DIABETES IN THE YOUNG: ORGANIZATION OF TWO NATIONAL CENTERS IN ISRAEL AND SLOVENIA

SLADKORNA BOLEZEN TIPA 1 PRI OTROCIH IN MLADOSTNIKIHI: ORGANIZACIJA DELA V DVEH NACIONALNIH CENTRIH V IZRAELU IN SLOVENIJI

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Received/Prispelo: Nov 5, 2014
Accepted/Sprejeto: Feb 3, 2015

Review article/Pregledni znanstveni članek

ABSTRACT

Keywords:

type 1 diabetes, children, metabolic control, reference centre, education, insulin pump, continuous glucose monitoring

Type 1 diabetes is a chronic autoimmune disease that affects mainly young people. In the last 50 years, a steady increase of the T1D incidence in the young is reported worldwide, with an average 4 % increase annually. In addition, the mean age at the diagnosis is decreasing. Studies show that good metabolic control is important not only for delaying the chronic complications of diabetes but also for improving the quality of life of patients and their families. Continuous education, together with modern technology, is crucial in achieving these goals. Longitudinal data on glycated hemoglobin (HbA1c), along with the data on severe hypoglycemia and severe diabetic ketoacidosis, can describe the quality of care in a defined population. Two national reference diabetes centres taking care of children, adolescents and young adults with diabetes in Israel and Slovenia are described.

IZVLEČEK

Ključne besede:

sladkorna bolezen tipa 1, otroci, presnovna urejenost, referenčni center, edukacija, inzulinska črpalka, neprekinjeno merjenje glukoze v podkožju

Sladkorna bolezen tipa 1 je kronično avtoimuno obolenje, ki najpogosteje prizadene mlade ljudi. Incidenca boleznih zadnjih 50 let narašča po vsem svetu, v povprečju je letni porast incidence ocenjen na 4 %, ob tem pa starost bolnikov ob času diagnoze pada. Raziskave kažejo, da je dobra presnovna urejenost bolnikov s sladkorno boleznijo zelo pomembna, saj je s tem mogoče odložiti pozne zaplete boleznih ter izboljšati kvaliteto življenja bolnikov in njihovih družin. Neprekinjena edukacija bolnikov skupaj z možnostmi moderne tehnologije lahko prispeva k izboljšanju njihove presnovne urejenosti. Presnovno urejenost spremljamo z določanjem glikoziliranega hemoglobina (HbA1c) ter s številom težkih hipoglikemij in ketoacidoz na populacijo pacientov v določenem časovnem obdobju. V prispevku sta opisana dva nacionalna referenčna centra za obravnavo otrok, mladostnikov in mladih odraslih s sladkorno boleznijo v Izraelu in Sloveniji.

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1 INTRODUCTION

Type 1 diabetes (T1D) is one of the most common chronic childhood diseases. In the last 50 years, a steady increase of the T1D incidence in children and adolescents is reported worldwide, with an average 4 % increase annually (1-5). In addition, the mean age at the diagnosis is decreasing (4-8). Accordingly, the educational and therapeutic approach of the diabetic team to a family with a child newly diagnosed with T1D is changing.

Already in the 1970s, the shortcomings of the accepted therapeutic approach handling diabetes strictly on the medical basis were recognized, noting the T1D treatment to be heavily burdensome for children (9).

Children and adolescents with T1D must not only learn to accept the fact that they differ from their peers, but also to coordinate the demands of their social framework (family, school, place of employment, leisure activities, sports) with those of the diabetic regimen (monitoring glucose levels, daily insulin administrations, and special diet maintenance). It soon became clear that a multidisciplinary team might best meet the needs of these young patients.

The changed approach resulted in the establishment of the Israel Counselling Centre for Juvenile Diabetics in 1976, introducing a comprehensive multidisciplinary approach within a specialized medical field to Israel. A similar approach led to the decision that all children with T1D should be treated centrally in Slovenia. The first child was treated in the University Children's Hospital Ljubljana (UCL) in 1956, while all Slovene newly diagnosed children and adolescents have been treated in UCL for the last 25 years. A multidisciplinary team and a structured educational program have been established (10, 11).

2 ORGANIZATION OF THE CLINICAL WORK

Today, the National Centre for Childhood Diabetes at the Institute of Endocrinology and Diabetes at Schneider Children's Medical Centre of Israel (SCMCI) is the national referral centre. It is the largest centre of the kind in Israel, and also one of the largest worldwide. The centre treats more than 1,600 patients with different types of diabetes annually, 100-120 of them newly diagnosed each year.

A holistic, multidisciplinary approach is practiced in the centre, accumulating valuable experience and expertise in the treatment of young people with diabetes.

The team is comprised of 8 senior pediatric endocrinologist, 3 fellows, 5 nurse educators, 4 dietitians, 2 social workers, and 3 psychologists. The staff is available on a 24-h basis, 7 days a week for calls. More than 6200

visits of patients with diabetes in the outpatient clinic are registered annually. The age of patients treated in this centre ranges between a few weeks and 30 years, with the same multidisciplinary team caring for children, adolescents, and young adults (Table 1).

Table 1. Descriptive data on patient population in Schneider's Children Medical Centre of Israel (SCMCI) and University Children's hospital Ljubljana (UCL), Slovenia.

	SCMCI	UCL
Incidence of T1DM (per 100.000)	12.2 (Jews), 8.9 (Arabs)	14.67
Average number of newly diagnosed children with T1D/year	120	60
Total number of patients	1600	650
Age range (years)	0-30	0-25
CSII users (%)	50	77
CGM users (%)	20	10
Medical team (number) physicians/nurses/psychologists/ dietitian/social worker	11/5/3/4/2	5/4/2/1/0.2
Education at diagnosis	Outpatient- based	In patient- based
Outpatient visits (number/year)	6200	3100
HbA1c (%) in 2000	8.3	9.26
HbA1c (%) in 2014	7.7	7.75

In Slovenia, the Department of Endocrinology, Diabetes and Metabolic Diseases at the UCL, is the national centre for childhood diabetes. Currently, over 650 patients with T1D and other rarer forms of diabetes (T2D, cystic fibrosis (CF) related diabetes, MODY, neonatal diabetes) are treated. Annually, up to 65 children with newly diagnosed T1D are referred from all parts of Slovenia, in addition to approximately 5 children with T2D and 1 with CF related diabetes. At the time, 3 senior pediatric endocrinologists, 2 fellows, 4 nurse educators, 1 dietitian, and 2 psychologists, partly also a social worker, are taking care of the whole population of patients. A 24/7-telephone line is provided to help patients or/and other physicians in case of problems with disease management or/and in emergencies. Around 3100 visits of patients with diabetes in the outpatient clinic are registered annually, with an average patient visiting the centre four times per year. The age of patients ranges between few weeks and 25 years (Table 1).

3 CLINICAL MANAGEMENT

In Israel, newly diagnosed patients with diabetes ketoacidosis (DKA) are usually hospitalized in the pediatric unit or intensive care unit (children younger than 2 years or patients with severe DKA) until correction of the DKA. Patients without DKA and without dehydration are usually discharged from hospitalization 1-2 days after their admission and some (e.g. those of older age, those with a first family member with diabetes) are usually discharged on the day of admission. On the first day of admission, a pediatric endocrinologist evaluates the child's state, confirms the diagnosis, outlines the therapeutic approach and sees the patient and his/her parents. On the same day, a dietitian, a nurse, and a member of the psychological team see the family. This intervention is usually performed on an ambulatory basis. The fact that therapy can be applied on an ambulatory basis can itself reduce the anxiety of the patient, and it poses fewer problems for both the patient and the family. Attention is paid to the cultural and educational background of the patient's family and their psychosocial and economic state. Medical and educational counselling are given to the patient and his family members.

In Slovenia, the initial approach to newly diagnosed T1D patients is predominantly based on a five-day hospital stay, where one parent stays with the child. In this period of time, the insulin regimen is stabilized - toddlers start with insulin pump treatment (CSII) immediately, while older children start with multiple daily injections (MDI). Certified nurse educators take care of the educational program. Patients and family members visit a dietitian, with the help of which eating habits are assessed and a nutritional plan is prepared. The family receives psychological support and advice; a pediatric endocrinologist explains basic facts about diabetes and its chronic complications.

In both countries, the goals of intensive management of T1D were implemented after the Diabetes Control and Complications Trial (DCCT) (12); the management strategy follows international guidelines (13). Patients with T1D and their caregivers continue to be challenged with having to maintain blood glucose levels in the near-normal range, having to prevent sustained hyperglycaemia associated with long-term microvascular and macrovascular complications, and having to avoid recurrent episodes of hypoglycemia. Intensified treatment can be achieved by more frequent visits at the diabetes clinic, or increased communication between patients and their medical-care team (14, 15). Thus, one of the most important factors in the long-term management of diabetes is the regulation of follow-up visit frequency. Patients are seen at least once every 3 months or more frequently if needed (in the first months after the diagnosis, when changing treatment

modality, and poorly controlled patients). The importance of the regular self-monitoring of blood glucose (SMBG) is repeatedly stressed to guide and monitor metabolic control. The SMBG should be performed at least 5-6 times a day. When a patient comes for the follow-up visits, the data from the glucometers and the insulin pump is downloaded to the hospital electronic record system. In the last years, the use of a web-based therapy management system (16), designed to simplify the information collection and assessment process and to help patients to communicate with their caregivers, is increasing.

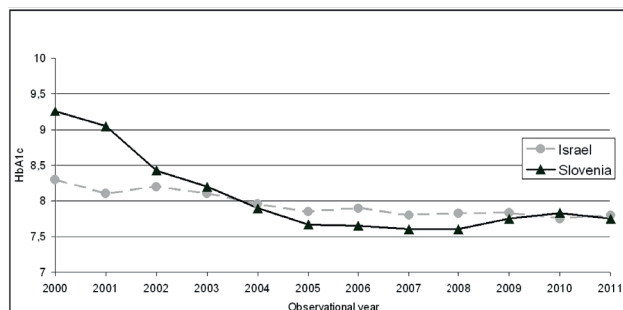
Adherence to an appropriate nutritional plan is another important part of the diabetes treatment regimen. The physician, nurse, and dietitian work together to attain an optimal diet, taking into account the age of the patient, her/his pubertal stage, amount of physical exercise, family habits and social/ethnic particularities (17). Patients/parents are instructed on how to calculate the carbohydrate and protein intake and how to adjust the insulin doses accordingly. In the first year after the diagnosis, patients consult the dietitian at every follow-up visit in Israel, while, in Slovenia, at least at the first follow-up visit and, subsequently, as needed. Thereafter, patients consult dietician twice a year or as required in Israel, while, in Slovenia, once yearly at a half-day follow-up visit, and possibly also during the summer camp.

One of the major obstacles in achieving and maintaining good metabolic control in T1D are the psychological problems that develop in both the affected child and his/her family members following the diagnosis of diabetes (18). Thus, in addition to the medical check-up, a psychologist and/or a social worker counsel the patient and his/her parents at least twice a year in Israel, and once a year in Slovenia. Additionally, a special intensified program was designed for children with suboptimal metabolic control, and a psychological support group for parents is available in Slovenia since 2009, where two psychologists lead group discussions on various important topics, such as partnership, living with a child with a chronic disease, emotional problems (19), etc. It seems that under the supervision and guidance of the multidisciplinary team, the child/adolescent with diabetes is able to lead a near-normal life in many, if not all, respects (20).

4 MONITORING GLYCEMIC CONTROL, SHORT- AND LONG-TERM COMPLICATIONS

Monitoring long-term glycaemic control is based on measuring HbA1c levels every 3 months in both centres. Capillary HbA1c is measured by an automated point-of-care immunoassay analyser (DCA Vantage Analyzer, Simens, Germany; reference range: 4.3-5.8%). Since the

beginning of the last decade, the annually measured average glycaemic control at the SCMCI has improved significantly with a decrease in the median HbA1c from 8.3% in 2000 to 7.7% in 2013 (21). Similarly, at UHCL, in the period between 2000 and 2012, the median HbA1c for the whole group of patients with all therapeutic regimens decreased from 9,26% to 7,75% (19) (Figure 1).



Legend:

Slovenia - University Children's Hospital Ljubljana

Israel - Schneider's Children Medical Centre of Israel

HbA1c - Glycated hemoglobin A1c

Figure 1. Metabolic control of children with type 1 diabetes over the last twelve years in the national reference centres in Slovenia and Israel.

Data on severe acute complications are recorded in the medical records. DKA is defined as an event requiring hospitalization and intravenous therapy, and severe hypoglycemia (SH) is defined as an event with a loss of consciousness and/or seizures, requiring hospitalization or glucagon injection, and/or intravenous glucose therapy (22, 23). At UHCL, the rates of these severe acute complications remain low at an average 1.54 per 100 patient-years for severe DKA, and 0.90 per 100 patient-years for SH (24).

In both centres, patients are followed annually for development of long-term microvascular complications by fundoscopic examination for detection of retinopathy and urinary analysis for microalbumin/creatinine. Patients are also followed annually for the development of associated other autoimmune diseases (celiac, autoimmune thyroiditis).

5 STRUCTURED STANDARDIZED EDUCATIONAL PROGRAM

The program in UHCL is based on a standardized step-by-step education for patients, family members and caregivers. Each step is recorded in the medical record, and the attained knowledge is verified with several written tests, which are also saved in the record. Slide sets and brochures are available.

- At the diagnosis: Parents and patients have a structured educational in-hospital program for 5 days. Infants and toddlers start with the pump treatment immediately.
- At the first outpatient visits (after 3-5 weeks): The family meets a pediatric endocrinologist, a dietitian, and a nurse educator, where the educational process is repeated in a half-day session.
- At CSII start: Technical and medical education is given on an outpatient basis. Pump providers organize technical education, a dietitian is teaching carbohydrate and protein counting, and certified nurse educators provide structured standardized CSII education and training (a standard set of slides and a brochure). Most of the eligible children start with the pump treatment six to nine months after the diagnosis.
- At CGM (sensor) start: A proper insertion of the sensor is discussed and practiced, along with correct calibration of the sensor and the use of different alarms (sensor-specific written material is provided). The family returns to the outpatient after six days for another sensor insertion and pump download - if they are afraid to insert the second sensor at home -, and/or after one month to see the first sensor download and discuss different problems that appeared.
- Education for teachers and other professional caregivers is given on individual or group basis. In the last 5 years, more than 300 teachers and other caregivers came annually to learn about diabetes in a one-day course, where they met all members of the team. A medical plan for each individual child is agreed, and preferably signed, during these educational sessions.
- Education for the first graders - children who enter the primary school are invited to a half-day educational session, where they learn about diabetes with the hospital teacher and a certified nurse educator. At the same time, parents are discussing how to make the school start as simple as possible: a pediatric endocrinologist, a certified nurse educator and a psychologist are present.
- A special educational opportunity is the summer camp, where 120 children aged from 6 to 15 years participate for two weeks to learn about diabetes and its practical management; young adult patients with T1D help the diabetes team in education and day-to-day care. Children have practical lessons on carbohydrates counting, they learn how to prepare some simple meals, repeat how to react in the case of low or high blood sugar, how to recognize DKA, they swim every day and engage in other sport activities. The first camp was organized in 1967, and ever since annually; all costs are covered by the national health insurance system.

- Yearly meetings for the families of children with diabetes have been organized since 1971. A special publication called 'Sladkorčki' ('Sweeties') is published covering various topics about good diabetes management along with patients' stories, reports and poems.
- Web site: The Society for Children with Metabolic Diseases, which works in close collaboration with the diabetes team at UCHL, has a web page since 2005 (<http://www.sladkorcki.si>), on which a lot of information about diabetes can be found. Information about different events is posted, as well as cooking recipes, useful links and telephone numbers (25, 26).

An important aspect of SCMCI's diabetes team activities is fostering ties between the staff, patients and their parents.

- A meeting of the multidisciplinary team with parents of children diagnosed with diabetes during the previous 6-month period is organized every 6-12 months to provide relief to parents recently faced with diabetes.
- Prior to the onset of the school year, the institute initiates the meeting between children with diabetes who are about to enter the first grade, together with their parents. The team and parents are sharing information.
- A series of meetings is held for patients who have difficulties coping with the diabetes of their children.
- SCMCI's diabetes team also organizes meetings with teachers and nurses from the children's schools in order to promote the understanding of the issues facing the child with diabetes at school.

6 IMPLEMENTATION OF DIABETES-RELATED TECHNOLOGIES

6.1 Patients Treated with CSII - Insulin Pump Therapy

Intensified insulin delivery usually consists of either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), and is based on self-monitoring of blood glucose (SMBG) and, recently, also on real-time continuous glucose monitoring (CGM).

The use of CSII is steadily increasing. At SCMCI, approximately 800 (50%) patients are treated with CSII, while, at UCHL, approximately 500 out of 650 (77%). In both centers, the multidisciplinary diabetes team recommends CSII therapy to eligible patients and/or their caregivers. The decision to initiate pump therapy is individualized and guided by the recommended indications for CSII therapy (27). If the patient/parents have a preference for CSII treatment, the issue is discussed with the diabetes team of the individual patient, and if there is no contraindication, the patient can start with CSII therapy (28, 29). A certified diabetes nurse educator and a dietitian conduct a 3-day

structured outpatients' education, along with technical training delivered by the pump provider. During the first month of CSII therapy, patients are asked to check blood glucose levels at least 8 times/day: before meals, 2 hours after meals, at bedtime, and at 2-3 a.m. Thereafter, the frequency is reduced to 6 times/day (without a regular night measurement). Insulin basal rates and correction boluses are adjusted as required at each follow-up visit, scheduled every 2-3 months, or during phone contacts. Patients are instructed to change infusion sets every 3 days, or more frequently if necessary.

6.2 Patients Treated with Continuous Glucose Monitoring (CGM)

Extensive evidence indicates that near-normalization of blood glucose levels is seldom attainable in children and adolescents after the remission period (30-32). Therefore, the development of CGM (33) may help children and adolescents with T1D improve their metabolic control (34, 35) and reduce the time spent in hypoglycemia (32, 36), as well as help their families to cope with the stress of day-to-day diabetes management (37-39).

At SCMCI, approximately 160 patients (20%) are treated with CGMs, while, at UCHL, roughly 60 patients (10%). The decision to use CGM is made jointly by the child/parents and diabetes team. The CGM is used either with MDI or CSII.

The connection to the CGM is usually done in patients with: evidence of severe hypoglycemic episodes, hypoglycemic unawareness, nocturnal hypoglycemia, and wide glucose excursions with suboptimal glycaemic control (HbA1c exceeding the target range). In Israel, sensors are reimbursed for the whole pediatric population; in Slovenia, sensors are completely reimbursed for children below the age of six, who represent the largest group of CGM users, but most of them continue to use the sensor also above this age (30).

Prior to connection to the CGM, a patient/family gets initial informations about CGM. A visit for CGM start-up, including instructions for insertion, site care, alarm setting, trend analysis, data analysis, etc. by a nurse practitioner, follows. After the period of 2-3 weeks, the data of the CGM is discussed with the physician in order to make the required changes in the diabetes management.

7 RESEARCH PROGRAM

Long-term metabolic outcome depends not only on excellence in, and dedication to, clinical care, but also on continuous clinical and basic research (12).

Both centres are intensively engaged in clinical research, ensuring their stay on the cutting edge of the latest innovations and advanced treatment modalities. Clinical

research includes diabetes-prevention trials (40), introduction of new drugs (41, 42) and new technologies (43, 44) for the treatment of diabetes, along with psychological investigations (45-47). Additionally, applied basic research conducted in both centres contributes to the knowledge on disease mechanisms (48-52). Both centres also participate in international data collection and benchmarking within the Centre of Reference SWEET project (53).

Diabetes Technology Centre dedicated to develop artificial pancreas, by closing the loop between CGM systems and pumps for CSII, was established at SCMCI. The Diabetes Technology team has developed a long-term clinical evaluation of the MD-Logic Artificial Pancreas System (MDLAP), which is based on the model that imitates the logic of diabetes care givers and allows individualized automatic glucose regulation based on CGM and CSII. The Diabetes Technology Institute is collaborating with prominent centres in the USA and Europe in the artificial pancreas project, and multicentre studies, in the effort to close the loop, are being carried out with diabetes centres in Slovenia and Germany. The MDLAP was evaluated in clinical trials performed in hospital (54), camp (55), and home (56, 57) settings. A routinely available artificial pancreas system will improve metabolic control and considerably lessen the burden of day-to-day diabetes management.

8 CONCLUSIONS

With the assistance of a dedicated, skilled and qualified multidisciplinary team, devoted parents and caregivers, and with the help of modern diabetes-related technology, young patients with diabetes can live a normal, active, successful and happy live. However, the dream and hope for a cure for diabetes remains vivid.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

The study was financed in part by EU-CDEC project number 2013-1-GB2-LEO-05-10755, and Slovene National Research Agency Grants J3-9663, J3-2412, J3-4116 and P3-0343.

ETHICAL APPROVAL

Ethical approval for this report was not required. The National Medical Ethics Committee approved the maintenance of the national T1D registry in Slovenia.

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