<u>REVIEW ARTICLE</u>

The Role of Nurses in Taking Care of Children With Type 1 Diabetes

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ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease leading to an insulin deficiency that causes hyperglycemia and associated symptoms. It is considered the most common type of diabetes, with the 4Ts (going to the toilet a lot, being really thirsty, feeling more tired than usual, losing weight or looking thinner than usual) being the most prevalent symptoms. Non-specific signs and symptoms are also possible, and delaying or missing the diagnosis can have a devastating effect on a child's health. Children with a definitive diagnosis of diabetes often require medical treatment for problems such as ketoacidosis, hypoglycemia and hyperglycemia. To reach glycated hemoglobin (HbA1c) values of 48 mmol/mol, lifetime rigorous monitoring and management of blood

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INTRODUCTION

T1D is a chronic autoimmune illness, which is defined by elevated levels of blood glucose (hyperglycemia) due to insulin insufficiency caused by pancreatic β -cell dysfunction. T1D is one of the most prevalent pediatric endocrine and metabolic disorders. The loss of β -cells is the effect of T1D on the autoimmune system in the great majority (70% to 90%) of patients, as it is linked with T1D and systemic autoantibodies. No immune response or autoantibodies can be glucose levels via insulin replacement treatment is needed in T1D.

Physical and psychosocial issues arise frequently with a diabetes diagnosis, resulting in poor management. Nurses play a significant role in detecting diabetes in a number of healthcare settings, resulting in quick diagnoses and prompt initiation of treatment. Not only do they provide critical assistance to help children and their families with the diagnosis, they also place particular emphasis on managing difficult days and common problems with ongoing management. Nurses can provide invaluable assistance managing this chronic condition by coping with day-to-day challenges. (*Altern Ther Health Med.* 2022;28(1):107-113)

found in a smaller percentage of patients.^{1,2} The reason for β -cell destruction in idiopathic type 1 or 1b diabetes is not understood. The development of autoantibodies is related to T1D several months or years before the symptoms manifest. Such autoantibodies are not considered pathogenic but act as indicators for autoimmune development. Target insulin, 65 kDa glutamic acid decarboxylase (GAD65; also known as glutamate decarboxylase 2), insulin-associated protein 2 (IA T2) or zinc transporting body 8 are auto-antibodies characteristically linked with T1D (ZNT8). Individuals with particular HLA genotypes, ie, HLA-to-DR and HLA-to-to-TDQ (HLADR-DQ), are more likely to develop 2 or more autoantibodies and type 2 diabetes.^{3,4} The first β -to-target auto-antibodies are often targeted against insulin or GAD65 (anti-insulin or anti-GAD65 auto-antibodies) during early childhood, although these auto anti-antibodies can both be present, while the IA or ZNT8 auto-antibodies are seldom seen initially. This issue is being studied in numerous trials in children who have been monitored since birth. The initial manifestation of β -cell targeted auto-antibodies is not apparent. T1D etiology was postulated as a continuum separated into phases related to antibody detection and development of β biscuit degradation, dysglycemia and

ultimate hyperglycemic symptoms. Etiology of cell-to-cell autoimmunity, which presumably comprises an environment-genetic combination of variables that trigger or enable an autoimmune reaction from β -cells, is yet to be defined.⁵⁻⁷ This occurs many years before dysglycemia and symptoms eventually arise.

In this study, we were looking at T1D, particularly autoimmune T1D, and the etiology, pathogenesis and post-progression phases.

LITERATURE SEARCH

The documents included in our study were obtained via a systematic electronic database search on Medline, EMBASE, CINAHL, PsycINFO and Web of Science. We created a search strategy with a professional medical library that uses current literature and combines the phrases and keywords of medical subject management (MeSH) related to our goal, population and technique. The SPIDER strategy to discover qualitative literature and search phrases was also shared with our surveys (sample, phenomena of interest, design, evaluation, kind of research). In order to find more information for inclusion, we examined the benchmarks of the included trials and pertinent reviews. Our search was confined to articles published after 2002, when flexible intensive insulin regimens were utilized extensively in regular clinical treatment.

ETIOLOGY

T1D is characterized by the immunologic destruction of islet β cells over months to years, ultimately resulting in an absolute insulin deficiency. Although the actual etiology is unknown, scientists propose that it is caused by a genetic predisposition linked to specific HLA (DR and DQ) alleles, namely DRB10401-DQB10302H and DRB103-DQB10201. Heritability is also determined by a number of additional genes.^{8,9} Without a family history, the chance of having T1D is approximately 0.4%; offspring of affected parents, 30%; children of affected fathers, 3% to 8%; and kids of affected mothers, 1% to 4%. The probability of inheriting T1D in identical twins over the first 10 years after the first twin's diagnosis is 30%, and lifetime risk is roughly 65%.¹⁰

The presence of circulating pancreatic auto-antibodies' indicates that a person is at risk of developing or has already developed T1D. Antibody against insulin (IAA), glutamate decarboxylase (GAD65), pancreatic islet cell cytoplasmic antibody (ICA), protein tyrosine phosphatase antibody (IA-2) or insulinoma related 2 and zinc transporter 8 (ZnT8) are present in the antibodies.¹¹ The chances of T1D development are directly proportionate to the number and titer of antibodies detected.

Viruses and other environmental factors are purported to induce apoptosis of autoimmune β cells in at risk individuals. T1D is more common in infants born to mothers who had coxsackievirus or another enterovirus during pregnancy according to many studies, which shows that toxic substances present in the environment also have an impact

on T1D development. According to the hygiene hypothesis, better sanitation is linked to a higher frequency of autoimmune-mediated illness.¹²⁻¹⁴ It has been claimed that a lack of appropriate immune system development occurs as a result of reduced early exposure to infectious microorganisms; dietary factors are also being considered as potential triggers. Consumption of bovine milk protein enhanced pancreatic islet autoimmunity development in study patients with low to medium risk HLA-DR genotypes, but there was no significant increase in risk in patients with high-risk genotypes.¹⁵

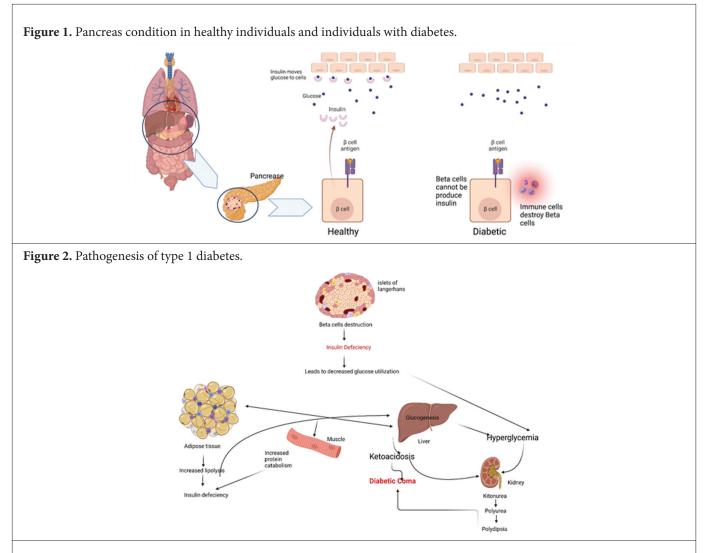
EPIDEMIOLOGY

T1D is reported to be most common chronic disease in children, although it can develop in anyone at any age. The incidence and prevalence of T1D is steadily increasing. Between 2001 and 2009, the prevalence of T1D increased by 21% in individuals younger than age 20 years.¹⁶ The most common age at symptom onset is from 4 to 6 years to age of precocious puberty (10 to 14 years). In the United States, there are an estimated 1.24 million patients with T1D, with the highest prevalence in non-Hispanic whites of both genders equally, and the number is expected to rise to 5 million by 2050.^{17,18} There is a lot of geographic variance in the occurrence of T1D around the globe. Finland and other Nordic nations have the highest number of recorded cases, which is almost 400 times greater than China and Venezuela, which have the lowest.¹⁹

PATHOPHYSIOLOGY

Development of T1D is a 3-step process. Normal glucose tolerance, normal fasting blood glucose levels and the presence of 2 or more pancreatic auto-antibodies indicate stage 1, which is asymptomatic. The presence of 2 or more pancreatic auto-antibodies along with glycemic abnormalities such as impaired glucose tolerance (140 to 199 mg/dL 2 hours post-prandial glucose level), fasting glycemic disorder (100 to 125 mg/dL glucose) or emoglobin A_{1c} between 5.7% and 6.4%, are all diagnostic criteria for stage 2 T1D and an individual will still be asymptomatic.^{20,21} Diabetes or hyperglycemia, along with its clinical signs, and 2 or more pancreatic auto-antibodies is considered to be stage 3 T1D²² (see Figure 1).

T1D in children is characterized by hyperglycemic symptoms, with diabetic ketoacidosis occurring in one-third of cases. Symptoms might appear abruptly after diagnosis, particularly in adolescents, which can lead to the requirement of emergency medical attention if T1D is not diagnosed and treated appropriately. Hyperglycemia with polyphagia, polydipsia are the most prevalent symptoms in patients with T1D. Polyuria is considered a secondary complication of hyperglycemia-induced osmotic diuresis.²³ Infants may have symptoms including nocturnal enuresis.^{24,25} Polydipsia is attributed to hyperosmolarity and dehydration as a result of excessive urination. As glucose causes osmotic swelling of the lenses of the eyes, it can induce blurred vision. In addition, there is generally a history of weight reduction. Along with



the breakdown of muscle and fat, there is a significant increase in lipolysis and ketone generation.²⁶ Overeating, lethargy, weakness and muscle wasting are all symptoms of this condition, and anomalies in electrolytes may also be observed. Patients will develop diabetic ketoacidosis (DKA) if these symptoms are not identified, necessitating hospitalization and intravenous fluids, insulin and potassium treatment, and continuous careful monitoring.²⁷

In adults, the development of T1D symptoms may be more varied. Diagnosis of diabetes can be made using either plasma glucose or HbA_{1c} criteria. If the patient has acute symptoms, plasma blood glucose should be obtained instead of HbA_{1c} for diagnosis because the patient's mean blood glucose level for the previous 2 to 3 months may not be abnormal. Patients with characteristic symptoms can be diagnosed with T1D if their random plasma glucose is >200 mg/dl.²⁸ A fasting plasma glucose level of \geq 126 mg/dl (excluding water, which is not consumed orally for at least 8 hours prior to testing) can also be used to diagnose diabetes. Oral glucose tolerance testing (OGTT) is uncommon, and a glucose level \geq 200 mg/dl is required after 2 hours of swallowing 75 g of anhydrous glucose for diagnosis.^{29,30} HbA_{1c} diagnosis criteria are \geq 6.5%, and Diabetes Control and Complications Trial assays are done in the

laboratory using techniques certified and standardized by the National Glycohemoglobin Standardization Program (NGSP). If the patient does not exhibit the usual signs of hyperglycemia or a hyperglycemic crisis, a second test should be performed to confirm the diagnosis (see Figure 2).³¹

THE ROLE OF THE NURSE IN DIAGNOSIS

Since nurses are in contact with children in many situations, they play an important role in identifying and diagnosing childhood diabetes.

Medical History

The key medical history that includes the 4Ts should be the basis of suspected diabetes evaluation in children. It should also include other indications, such as headache, constipation and vulvar thrush.³² This is especially important in babies with underlying diabetes who may have non-specific symptoms. Because older children may not want to discuss difficulties like bedwetting or dropping out of school in front of their parents, it may be better to speak with them alone (see Table 1).³³

Examination

Diabetes must be recognized as a differential diagnosis because nurses working in various healthcare systems will encounter children with varying indications. The tests are usually performed by a healthcare professional or a hands-on or emergency medicine nurse. It is vital to record important variables and check blood glucose levels.³⁴⁻³⁶ It is not recommended to wait for a urine sample to test for diabetes, as this will delay the diagnosis and prevent the development of DKA. Managing DKA is critical; emergency room nurses are likely to encounter DKA in children with severe diabetes, who should be triaged based on their current medical condition before undergoing routine testing and evaluation:³⁷

- AVPU: Alert, Voice, Pain, Unresponsive
- Vital signs: temperature, respiratory rate, blood pressure, heart rate and central capillary refill time
- Record blood glucose and ketone levels
- Pediatric Glasgow Coma Scale (GCS) for thorough assessment of consciousness level

Dehydration causes a decline in blood pressure in DKA, which is generally a delayed symptom. Acidosis induces an increase in respiration and a deepening of the breath. Children who are unwell need to be urgently evaluated by a pediatrician, and management of the child should be done according to the hospital pediatric department's DKA approach or guidelines of the British Paediatric Endocrinology and Diabetes Society.³⁸ Fatal complications of DKA include cerebral edema, usually caused by excessive infusion and manifest by decreased GCS level, headaches, bradycardia, and disorientation.

THE ROLE OF NURSES IN INVESTIGATIONS

Children with diabetic indications should have their blood glucose levels checked on a regular basis. When blood sugar levels reach 11 mmol/L (with no other cause) (National Institute for Health and Care Excellence [NICE], 2016), diabetes is diagnosed. When testing blood sugar, the child's hands must be completely cleaned and dried before obtaining a drop of blood in order to obtain an accurate measurement.³⁹ It is critical not to wait for the child's glucose tolerance test and fasting blood glucose level since during this period DKA may develop.

Nurses can assist by coordinating additional investigations:

- **Blood glucose levels**: Required to establish whether blood glucose levels have risen or fallen, and also the level of diabetes present.
- **Plasma and urine ketone levels**: Can help distinguish DKA from hyperosmolar disease, which is treated differently.
- **Blood gas**: To detect the blood acidity level, and important for identifying whether or not DKA is present.
- Complete blood count and C-reactive protein: Performed to rule out the possibility of infection.

Table 1. The Four Ts of Diabetes

Toilet	Polyuria is the need to use the restroom more often, which is the most prevalent sign of diabetes in children. Because bedwetting recurrence is rather prevalent in older children, and because children and/or parents may not readily offer information, the nurse should approach the child personally.
Thirsty	Polydipsia is the desire to consume excess liquids. This may be a difficult-to-diagnose symptom; for example, consuming extra water in hot weather may be considered normal, and grownup independent children may be unaware of an alteration in their drinking habits.
Tired	Still feeling tired after enough sleep. Individuals may awaken several times during the night to urinate. People will feel tired if insulin is lacking as glucose cannot enter the muscle cells. Children may start to miss school or stop participating in organized sports and exercise.
Thinner	Weight loss can be difficult to quantify. However, parents may be able to determine whether a child has lost weight by their clothes becoming looser.

Gastroenteritis, lung infections and urinary tract infections can all be misdiagnosed as childhood diabetes.

- **Urea and electrolytes**: Evaluates kidney function; is likely to be abnormal in dehydrated individuals.
- Celiac disease screening and thyroid function testing: Identifies additional autoimmune disorders that may be present.
- Screening of diabetes-specific auto-antibodies or C-peptide titres: can be done later if the pediatric diabetes experts think it's necessary.⁴⁰

Treatment

Children with recently diagnosed diabetes or DKA should be treated in the hospital pediatric ward, or if more serious in a pediatric intensive care unit (PICU) or high dependency unit (HDU). The primary objective of diabetes treatment is to stabilize blood sugar levels with vigorous insulin therapy and, if the child is in DKA, to restore fluid and electrolyte balance. Hospital nurses are usually involved at this management stage,⁴¹ when repeat blood tests and the recording of important parameters (blood pressure, heart rate, body temperature and respiratory rate), blood sugar and ketone management, insulin and intravenous fluids management is needed (NICE, 2016).

The purpose of long-term management is to measure blood glucose levels when the HbA_{1c} is <48 mmol/mol and get it as close to normal as possible (NICE, 2016). This requires diabetes education for both the children and their families, including insulin management, carbohydrate counting and maintenance of a healthy lifestyle.⁴² From the time of diagnosis, social and psychological support is vital, as diabetes is a life-changing illness not only for the patient but for the whole family. Children who are struggling to control their blood sugar levels also need other help and support. The overall goal of therapy is to allow patients to manage their disease in a way that has the least impact on their quality of life.⁴³

Diabetes Education

Once pediatric diabetes is diagnosed, the child and their family should be able to start managing their condition immediately after leaving the hospital and returning home. To begin the process, they need to learn about insulin usage, carbohydrate counting and blood sugar and ketone monitoring.⁴⁴ Recently diagnosed patients, after admission, should be sent to a well-trained pediatric diabetes nurse specialist (PDSN) as soon as possible for initial instructions and also for frequent future blood glucose joint examinations. Families need to learn the "sick day" rules: (1) continue taking insulin and diabetes medications as usual, (2) test blood sugar every 4 hours and keep a record of the results, (3) drink extra calorie-free liquids and try to eat normally and (4) weigh the child every day.

Insulin

Insulin can be administered by subcutaneous injection multiple times a day, or by continuous subcutaneous injection via insulin pump. Multiple daily injections are used to restore healthy pancreatic function by supplying a baseline amount of insulin plus an extra bolus before meals to help regulate blood sugar levels.⁴⁵ Insulin can be administered via injection into the abdominal wall of the buttocks, the outer thigh or the upper outer quadrant. Safe injection procedures must be taught to both children and their parents. Although better blood sugar control can be achieved by continuous infusion, the pump may present practical challenges leading to hyperglycemia or hypoglycemia, so the child's health and fitness should also be evaluated regularly.46 It is important for the child/parents to change the insulin injection site for each dose as repeated use of the same site can cause fat tissue to clump in the scar tissue. Insulin absorption in these areas is unstable, leading to poor blood sugar control.

Carbohydrate Counting

Assessing food's carbohydrate content is crucial for both children and their parents to master, and proper training is vital. They can use the carbohydrate count to directly match the child's insulin dose to the amount of carbohydrates the child consumes. This provides the child with more flexibility, because they can adjust their insulin dose to their desired diet instead of eating a set amount.⁴⁷ Using the selected insulin-carbohydrate ratio, pre-meal insulin is adjusted depending on the predicted insulin-carbohydrate ratio contained in the diet and snacks (NICE, 2016). For adolescents and children with T1D, their families and caregivers, daily use of multiple insulin injection regimens is necessary before (but not after) taking fast-acting insulin analogs to lower their blood sugar, help optimize post-prandial levels and maintain blood sugar control (NICE, 2015).⁴⁸

Blood Glucose Monitoring

Children should measure blood glucose levels at least 5 times every day, and HbA_{1c} should be kept below 48 mmol/mol (6.5%) for long-term blood sugar management

(NICE, 2016). Nurses must be vigilant about children having difficulty maintaining blood sugar levels, and children may require more education and intervention for better management. Continuous blood glucose monitoring may be required for children who have recurrent episodes of hypoglycemia or who are unable to verbalize hypoglycemic episodes owing to cognitive or neurologic impairment.⁴⁹ Kits for blood ketone monitoring should also be given to children (or their families) for use during sickness or hyperglycemic episodes. This enables early detection of DKA symptoms and prompt treatment (NICE, 2015). The following are the recommended goal ranges for short-term blood glucose management in children and young people with T1D and their family members or caregivers (NICE, 2015):

- Upon awakening (fasting condition): 4 to 7 mmol/liter
- At other times of the day before meals (pre-prandial): 4 to 7 mmol/liter
- After meals (at least 90 minutes) (post-prandial): 5 to 9 mmol/liter
- When driving: ≥5 mmol/liter

Community Support

Nurses should educate family members about the numerous types of community support available. The British Diabetes Association, for example, organizes local support groups all around the UK where parents can meet and discuss their diabetes experiences. On weekends, British Diabetes Association members travel and make presentations to keep youngsters happy and active while learning more about diabetes. Children and adults can get insight and peace of mind from others who have faced similar challenges by participating in online communities.⁵⁰

Diet and Exercise

According to studies, regular exercise does not enhance blood sugar management, but does lessen the risk for future cardiovascular issues. A diet rich in fruits, vegetables and low-glycemic carbohydrates is good for blood sugar control and overall health. Current evidence suggests that the use of motivational interviews and patient-centred counselling methods is the most effective method for achieving sustained lifestyle changes (Scottish Intercollegiate Guidelines Network [SIGN], 2013).⁵¹ It is a good idea to start by understanding the treatment options that a family thinks can be achieved. Then, if changes need to be made, the family can be involved in planning and setting goals, enabling them to be active in the management of children's diabetes levels.

Social and Psychological Support

Diabetes therapy includes focusing on mental wellness; anxiety and depression are more common in children with diabetes, which can contribute to poor blood sugar management (NICE, 2016). Various studies suggest that persistently poor blood sugar management is a potential factor for inducing psychotic incidents.⁵² Some patients have poor blood sugar management, which puts them at a higher risk for complications. Children with divorced parents, from underprivileged homes, under the care of children or having learning difficulties are all examples of children with learning difficulties. For children who cannot control their blood sugar levels well, screening for depression and anxiety is essential. Family members need to understand the support provided by mental health services and consult them immediately when needed.

Management of Adolescent Diabetes. This is a challenge for healthcare providers, because adolescents are at a higher risk for poor diabetes management owing to changes in their social interactions, physiology and family dynamics.⁵³ Although it is critical to begin allowing independence and encouraging young people to take responsibility for their diabetic condition, various studies show that patients having difficulty managing their diabetes are more likely to react to behavioral interventions. However, as time goes by, this influence tends to diminish, and the regular support of a PDSN and the use of information technology may help improve compliance.

Diabetes control will be improved with active family support and a thorough knowledge of diabetes and its related implications. Blood sugar control, the potential impact of a long-term high HbA_{1c}, the impact of "hypos" and "hypers," and information that was developmentally suitable for young people and their parents was presented in a seminar and was the subject of a British study of 22 families.⁵⁴ The study found that young people like to share ideas and meet other people with diabetes, and parents like to listen to their children talking about their knowledge of diabetes (see Table 2).

THE ROLE OF PEDIATRIC DIABETES SPECIALIST NURSES

PDSNs are critical in the management of diabetic conditions in youngsters, and have expertise in the management, counseling and education of children with diabetes and their families. Without this expertise, it is difficult to deliver a comprehensive strategy. Clinics managed by PDSNs are increasingly being shown to be as successful as clinics managed by doctors. Diabetes management approaches should not just focus on HbA_{1c} levels, but also on coping and motivating tactics, since this is critical for reaching optimal treatment goals.55,56 Application of psychosocial constructs by PDSNs can assist children and their parents in better comprehending diabetes on a social and personal level. This has a favorable impact on the family's attitude toward therapy, resulting in better diabetes management. The proper treatment of pediatric diabetes requires family-centred treatment based on the child's individual requirements and lifestyle and a full-time PDSN is responsible for establishing this.57 With a PDSN's ongoing assistance, it easier to keep track of each child's specific requirements. When children learn to manage diabetes on their own, they are at the unstable stage of disease management.58

CONCLUSION

T1D is a prevalent chronic condition in children that requires lifetime care and assistance from a variety of healthcare professionals. PDSNs can assist in the early diagnosis of pediatric T1D, as well as long-term management, and to avert medical emergencies, early diagnosis and treatment of DKA are critical. 4T awareness is highly useful in detecting early indicators of diabetes. Education and awareness is essential,

Table 2. The Role of Nurses in the Management of Diabetes in Children and Adolescents

Clinical Setting	Role in Diabetes Management
Emergency Room Nurses	 Note whether children who are diagnosed with T1D have signs of 4T and/or DKA Request emergency medical evaluations for children with diabetes-related or suspected diabetes-related problems If the nurse suspects that a child has diabetes, perform a blood sugar test, and if blood sugar is >11 mmol/L, make a quick referral Support DKA for child recovery and keep family members informed of latest developments Update the PDSN who will participate in the emergency department in a child with T1D for problems related to diabetes such as a sudden lack of insulin reserves, hypo- or hyperglycemia
Pediatric Nurses	 Recognize the symptoms and indicators of child's hyperglycemic condition before the onset of DKA Monitor the vital indicators and Pediatric Early Warning Score (PEWS) of children with DKA Understand that autoimmune status applies across the board and to be on the alert for celiac disease and hypothyroidism Support children and their families who have been diagnosed with diabetes and hospitalized Work closely with the PDSN to optimize diabetes education
School Nurses	 Identify the 4Ts and refer child to healthcare professionals as soon as possible Support the school's blood glucose monitoring and subcutaneous insulin injection protocol after diagnosis Emphasize PDSN issues such as low enrollment rate, high blood sugar control and instability Ask staff, especially physical education teachers, to pay attention to the symptoms of hypoglycemia Provide support and arrange meetings with school counsellors as needed
Practice Nurses in GP Offices	 If parents are bringing children in due to bedwetting recurrence, non-specific abdominal pain or increased drinking water intake, consider the possibility of diabetes Parents of babies who notice "heavy diapers" (ie, large volumes of urine) should consider diabetes a possibility Maintain a supply of insulin and other related products to track blood sugar and ketones Ascertain that both parents and children are aware of the significance of diabetes and blood sugar management Ascertain that parents and children are aware of the signs and symptoms of hypo-, hyperglycemia and DKA

Abbreviations: DKA, diabetic ketoacidosis; GP, general practitioner; PDSN, Pediatric Diabetes Specialist Nurse; T1D, type 1 diabetes.

and may be accomplished with the help of a PDSN and other nurses. The value of motivational interviewing and the use of psychosocial composition in accomplishing therapeutic goals is becoming increasingly evident.

REFERENCES

- 1. Barnett R. Type 1 diabetes. Lancet. 2018;391(10117):195.
- Beck RW, Bergenstal RM, Laffel LM, Pickup JC. Advances in technology for management of type 1 diabetes. *Lancet.* 2019;394(10205):1265-1273.
- Chellappan DK, Sivam NS, Teoh KX, et al. Gene therapy and type 1 diabetes mellitus. *Biomed Pharmacother*. 2018;108:1188-1200.
- Craig ME, Kim KW, Isaacs SR, et al. Early-life factors contributing to type 1 diabetes. *Diabetologia*. 2019;62(10):1823-1834.
- Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. *Lancet*. 2019;394(10205):1286-1296.
- De Beaufort C, Besançon S, Balde N. Management of type 1 diabetes. Med Sante Trop. 2018;28(4):359-362.
- Desai S, Deshmukh A. Mapping of type 1 diabetes mellitus. Curr Diabetes Rev. 2020;16(5):438-441.
- Bělobrádková J. Pregestional diabetes mellitus and pregnancy. Vnitr Lek. 2016;62(11 Suppl 4):S26-S29.
- Bimstein E, Zangen D, Abedrahim W, Katz J. Type 1 diabetes mellitus (juvenile diabetes) - A review for the pediatric oral health provider. J Clin Pediatr Dent. 2019;43(6):417-423.
- Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus. Curr Opin Pediatr. 2017;29(2):199-205.
- Calliari LE, Almeida FJ, Noronha RM. Infections in children with diabetes. J Pediatr (Rio J). 2020;96(Suppl 1):39-46.
- Cameron FJ, Northam EA, Ryan CM. The effect of type 1 diabetes on the developing brain. *Lancet Child Adolesc Health*. 2019;3(6):427-436.
- Gautam RK, Sharma S, Sharma K, Gupta G. Evaluation of antiarthritic activity of butanol fraction of Punica granatum Linn. Rind extract against Freund's complete adjuvant-induced arthritis in rats. J Environ Pathol Toxicol Oncol. 2018;37(1):53-62.
- Kazmi I, Rahman M, Afzal M, et al. Anti-diabetic potential of ursolic acid stearoyl glucoside: a new triterpenic gycosidic ester from Lantana camara. *Fitoterapia*. 2012;83(1):142-146.
- Castellanos L, Tuffaha M, Koren D, Levitsky LL. Management of diabetic ketoacidosis in children and adolescents with type 1 diabetes mellitus. *Paediatr Drugs*. 2020;22(4):357-367.
- Costa-Cordella S, Luyten P, Giraudo F, Mena F, Shmueli-Goetz Y, Fonagy P. Attachment and stress in children with type 1 diabetes and their mothers. *Rev Chil Pediatr.* 2020;91(1):68-75.
- Devi B, Kumar Y, Shrivastav B, Sharma GN, Gupta G, Dua K. Current updates on biological and pharmacological activities of doxycycline. *Panminerva Medica*. 2018;60(1):36.
- Gupta G, Dahiya R, Singh Y, et al. Monotherapy of RAAS blockers and mobilization of aldosterone: a mechanistic perspective study in kidney disease. *Chem Biol Interact.* 2020;317:108975.
- Czenczek-Lewandowska E, Grzegorczyk J, Mazur A. Physical activity in children and adolescents with type 1 diabetes and contemporary methods of its assessment. *Pediatr Endocrinol Diabetes Metab.* 2018;24(4):179-184.
- 20. Elder CJ, Dimitri PJ. Diabetes insipidus and the use of desmopressin in hospitalised children. *Arch Dis Child Educ Pract Ed.* 2017;102(2):100-104.
- Evia-Viscarra ML, Guardado-Mendoza R, Rodea-Montero ER. Clinical and metabolic characteristics among Mexican children with different types of diabetes mellitus. *PLoS One.* 2016;11(12):e0168377.
- Gupta G, Dua K, Kazmi I, Anwar F. Anticonvulsant activity of Morusin isolated from Morus alba: Modulation of GABA receptor. *Biomed Aging Pathol.* 2014;4(1):29-32.
- Fox LA, Hershey T, Mauras N, et al. Persistence of abnormalities in white matter in children with type 1 diabetes. *Diabetologia*. 2018;61(7):1538-1547.
- 24. Gupta G, Singh Y, Tiwari J, et al. Beta-catenin non-canonical pathway: A potential target for inflammatory and hyperproliferative state via expression of transglutaminase 2 in psoriatic skin keratinocyte. *Dermatol Ther.* 2020;33(6):e14209.
- Gupta G, Singhvi G, Chellappan DK, et al. Peroxisome proliferator-activated receptor gamma: promising target in glioblastoma. *Panminerva Medica*. 2018;60(3):109-116.
- Friedman DN, Tonorezos ES, Cohen P. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr.* 2019;91(2):118-127.
- Hamilton H, Knudsen G, Vaina CL, Smith M, Paul SP. Children and young people with diabetes: recognition and management. Br J Nurs. 2017;26(6):340-347.
- Iminger-Finger I, Kargul J, Laurent GJ. Diabetes: Present and future. Int J Biochem Cell Biol. 2017;88:196.
- Kallinikou D, Soldatou A, Tsentidis C, et al. Diabetic neuropathy in children and adolescents with type 1 diabetes mellitus: Diagnosis, pathogenesis, and associated genetic markers. *Diabetes Metab Res Rev.* 2019;35(7):e3178.

- Kumar Chellappan D, Yenese Y, Chian Wei C, Gupta G. Nanotechnology and diabetic wound healing: a review. *Endocr Metab Immune Disord Drug Targets*. 2017;17(2):87-95.
- Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. JAMA. 2020;324(8):801-804.
- 32. Maurya H, Dhiman S, Dua K, Gupta G. Pharmacological effect of berberine chloride in propylthiouracil induced thyroidal dysfunction-a time bound study in female rats. *Rec Patents Drug Delivery Formulat*. 2016;10(2):165-173.
- Kharode I, Coppedge E, Antal Z. Care of children and adolescents with diabetes mellitus and hyperglycemia in the inpatient setting. *Curr Diab Rep.* 2019;19(10):85.
- 34. Lawnicki J, Hansdorfer-Korzon R, Myśliwiec M. Alterations in postural control, gait pattern, and muscle function in diabetes mellitus: does it matter in children and adolescents with type 1 diabetes? *Pediatr Endocrinol Diabetes Metab.* 2019;25(1):23-27.
- Pradhan R, Singhvi G, Dubey SK, Gupta G, Dua K. MAPK pathway: a potential target for the treatment of non-small-cell lung carcinoma. *Future Med Chem.* 2019;11(8):793-795.
- Samuel VP, Gupta G, Dahiya R, Jain DA, Mishra A, Dua K. Current update on preclinical and clinical studies of resveratrol, a naturally occurring phenolic compound. Crit Rev Eukaryot Gene Exprs. 2019;29(6):529-537.
- Lipman TH, Willi SM, Lai CW, Smith JA, Patil O, Hawkes CP. Insulin pump use in children with type 1 diabetes: Over a decade of disparities. *J Pediatr Nurs*. 2020;55:110-115.
- Neu A, Bürger-Büsing J, Danne T, et al. Diagnosis, therapy and follow-up of diabetes mellitus in children and adolescents. *Exp Clin Endocrinol Diabetes*. 2019;127(S 01):S39-S72.
- Panagiotopoulos C, Hadjiyannakis S, Henderson M. Type 2 diabetes in children and adolescents. *Can J Diabetes*. 2018;42(Suppl 1):S247-S254.
- Patti G, Ibba A, Morana G, et al. Central diabetes insipidus in children: Diagnosis and management. *Best Pract Res Clin Endocrinol* Metab. 2020;34(5):101440.
- Peña AS, Curran JA, Fuery M, et al. Screening, assessment and management of type 2 diabetes mellitus in children and adolescents: Australasian Paediatric Endocrine Group guidelines. *Med J Aust.* 2020;213(1):30-43.
- Pierce JS, Kozikowski C, Lee JM, Wysocki T. Type 1 diabetes in very young children: a model of parent and child influences on management and outcomes. *Pediatr Diabetes*. 2017;18(1):17-25.
- Pillay S, Anderson J, Couper J, Maftei O, Gent R, Peña AS. Children with type 1 diabetes have delayed flow-mediated dilation. *Can J Diabetes*. 2018;42(3):276-280.
- 44. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care*. 2020;43(11):2870-2872.
- Rankin D, Harden J, Jepson R, Lawton J. Children's experiences of managing type 1 diabetes in everyday life: a thematic synthesis of qualitative studies. *Diabet Med.* 2017;34(8):1050-1060.
- Rearson M, Sullivan-Bolyai S. Management of type 1 diabetes in children in the first 5 years of life. *Pediatr Endocrinol Rev.* 2017;14(Suppl 2):412-421.
- Rechenberg K, Grey M, Sadler L. Stress and posttraumatic stress in mothers of children with type 1 diabetes. J Fam Nurs. 2017;23(2):201-225.
- Rughani A, Friedman JE, Tryggestad JB. Type 2 diabetes in youth: The role of early life exposures. *Curr Diab Rep.* 2020;20(9):45.
- Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: Recognition and treatment options. *Curr Diab Rep.* 2018;18(8):58.
- Saydah S, Imperatore G, Cheng Y, Geiss LS, Albright A. Disparities in diabetes deaths among children and adolescents - United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2017;66(19):502-505.
- Schernthaner-Reiter MH, Stratakis CA, Luger A. Genetics of diabetes insipidus. Endocrinol Metab Clin North Am. 2017;46(2):305-334.
- Temneanu OR, Trandafir LM, Purcarea MR. Type 2 diabetes mellitus in children and adolescents: a relatively new clinical problem within pediatric practice. J Med Life. 2016;9(3):235-239.
- Yarhere IE, Jaja T, Anolue M. Microalbuminuria in type 1 diabetes mellitus children in University of Port Harcourt Teaching Hospital, Nigeria. Pan Afr Med J. 2020;36:161.
- Ziegler R, Neu A. Diabetes in childhood and adolescence. Dtsch Arztebl Int. 2018;115(9):146-156.
- 55. Allen D. The nurse's role in childhood diabetes. Nurs Child Young People. 2016;28(10):11.
- Döğer E, Bozbulut R, Soysal Acar A, et al. Effect of telehealth system on glycemic control in children and adolescents with type 1 diabetes. J Clin Res Pediatr Endocrinol. 2019;11(1):70-75.
- 57. Feeley CA, Sereika SM, Chasens ER, et al. Sleep in parental caregivers and children with type 1 diabetes. J Sch Nurs. 2019:1059840519865942.
- Fornari E, Maffeis C. Treatment of metabolic syndrome in children. Front Endocrinol (Lausanne). 2019;10:702.