Review and Update of Insulin Dependent Diabetes Mellitus

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The purpose of this article is to provide the health care practitioner with a comprehensive review of the pathophysiology and treatment of Type 1 Diabetes Mellitus. Traditionally, insulin has been administered via an insulin syringe. In the recent past, diabetes research has focused on developing more convenient insulin delivery devices and longer acting insulin's in hopes of increasing compliance with insulin therapy and improving the management of Type 1 diabetes in both children and adults. Rapidly developing approaches to insulin delivery for Type 1 diabetes continue to be developed at a rapid rate, including administration via continuous subcutaneous insulin infusion in addition to other new approaches. With these advances in therapy, pediatric patients with Type 1 diabetes have been able to achieve strict glycemic control, although the treatment of hypoglycemia remains a burden. The objectives of this article are to the following: to review the epidemiology, risk factors, pathophysiology, clinical manifestations, and diagnostic criteria of Type 1 diabetes mellitus in children,; to discuss the management of these patients, including, insulin therapy, monitoring, diet and exercise, carbohydrate counting and treatment of hypoglycemia,; and to review insulin administration devices, including insulin pens, insulin jet injectors, insulin pumps, and novel insulin delivery systems.

KEYWORDS: diabetes, Type 1 Diabetes, insulin dependent diabetes, insulin, insulin administration, insulin devices, blood glucose

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Abbreviations

ADA	American Diabetes Association
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
FPG	Fasting plasma glucose
GAD ₆₅	Glutamic acid decarboxylase
HbA _{1c}	Hemoglobin A _{1c}
IAA	Insulin autoantibodies
ICA	Islet cell antibodies

INTRODUCTION

Diabetes mellitus is a group of autoimmune, metabolic diseases, which are characterized by hyperglycemia, resulting in impaired insulin secretion, insulin action, or both.¹ The majority of cases can be divided into two broad categories: Type 1 and Type 2. Type 1 diabetes, formerly

referred to as juvenile onset or insulin-dependent diabetes mellitus, is caused by an inability to secrete insulin. These cases are due primarily to pancreatic islet b-cell destruction in patients who are prone to ketoacidosis.¹ Type 2 diabetes, formerly referred to as adult onset or non-insulin dependent diabetes mellitus, is a result of insulin resistance and the presence of an insulin secretory defect. In addition to meeting other objectives, this article will review the epidemiology, risk factors, pathophysiology, clinical manifestations, and diagnostic criteria of Type 1 diabetes mellitus in children. The manuscript will also review the management of these patients, including insulin therapy, monitoring, diet and exercise, carbohydrate counting and treatment of hypoglycemia. Furthermore, the article will review insulin administration devices including insulin pens, insulin jet injectors, insulin pumps, and novel insulin delivery devices. Discussions of Type 2 diabetes and diabetic ketoacidosis (DKA) are outside the scope of this article and, therefore, will not be addressed.

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EPIDEMIOLOGY

In the United States, the reported prevalence rate of Type 1 diabetes is 1.7 children per 1,000, making this disease the second most common chronic childhood disease behind asthma.² It has been estimated that there are more than 130,000 children with Type 1 diabetes in the United States alone, with 13,000 new cases diagnosed annually.³ Additionally, there does appear to be a strong association between age and prevalence. Although 75% of children who develop Type 1 diabetes will do so by their 15th birthday, 1 in 2,500 children and 1 in 300 individuals will be diagnosed by 5 and 18 years of age, respectively.⁴ The male to female incident rates are equal.⁵

RISK FACTORS

It is widely accepted that Type 1 diabetes has a strong genetic component. This has been shown in several studies evaluating both monozygotic and dizygotic twins. Concordance approaches 50% for Type 1 diabetes in identical twins, but only 30% in fraternal twins.⁶ Because not all monozygotic twins are affected equally, only the susceptibility to Type 1 diabetes is inherited, not the disease itself. If a father has Type 1 diabetes, there is a 4%-6% risk of his children developing the disease.⁴ This risk falls to 2%-3% for children of diabetic mothers.⁴ The overall risk of a child developing Type 1 diabetes when one parent is affected is 5%.⁴

Certain genetic alterations occur within the human leukocyte antigen (HLA) region of chromosome 6 that may raise or lower one's risk of β -cell damage and subsequent development of Type 1 diabetes.⁷ The inheritance of human leukocyte antigen (HLA) halotypes DR3 and DR4 is associated with a three- to ten-fold increased risk of developing Type 1 diabetes as compared to controls who do not possess these markers.⁷ Approximately 95% of all patients diagnosed with Type 1 diabetes have DR3, DR4, or both antigens present on chromosomal analysis.⁵

While genetic factors play a major role in the development of Type 1 diabetes, variance seen among first-degree relatives suggests that environmental factors must also be taken into consideration.⁴ As a result of these insults, there is autoimmune destruction of the pancreatic b-

cells.⁴ This is evidenced by lymphocytic infiltration in the islet cells of new patients, specificity of β -cell destruction, and the presence of antibodies specific for islet antigens.⁴

Environmental triggers may include either recurrent or intermittent exposure or continuous exposure over a long period of time.⁶ Due to seasonal variability in diabetes and the widespread occurrence of diabetes 4 to 5 years following viral epidemics, viruses have been strongly implicated in the development of Type 1 diabetes.⁴ Associated viruses include mumps, Coxsackie B4, and other enteroviruses.⁷ Other triggers associated with the development of Type 1 diabetes include both infant and maternal nutrition. Early weaning from breastmilk and the early institution of cows' milk and solid foods have been implicated.⁴ Maternal consumption of smoked foods, which are rich in nitrates, nitrites, and nitrosoamines, provide free radicals that can damage fetal β -cells and initiate the autoimmune response, leading to the development of Type 1 diabetes later in the infant's life.⁴

The autoimmune process leads to a release of cytokines, which destroy pancreatic β -cells either directly or through the generation of free radicals.⁷ Interleukin-1, tissue necrosis factor, and interferon gamma also have roles in this degradation process.⁵ This has led many investigators to believe there are two phases in β -cell destruction: an early cytokine-dependent initiation phase and a late phase, antigen-specific, T lymphocyte proliferation, which amplifies and perpetuates cell destruction.⁷ This destruction of b-cells in the pancreas is marked by the presence of islet cell autoantibodies (ICA's), autoantibodies to insulin (IAA's), autoantibodies to glutamic acid decarboxylase (GAD₆₅), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β .¹ One or more of these autoantibodies are present in approximately 90% of all newly diagnosed patients with Type 1 diabetes.¹

In Type 1 diabetes, the rate of b-cell destruction is variable and directly related to age, being more rapid in infants and children and slower in adults. In patients <7 years of age, 80% of islet cells are damaged at diagnosis.⁴ This value decreases to 60% in children who are 7-14 years of age at diagnosis, and to 40% in those over 14 years of age.⁴ In young children, destruction is complete within 3 years of diagnosis, while 15% of older patients retain some degree of b-cell

function for up to 10 years.⁴ This suggests that b-cell autoimmunity is well developed by 7 years of age and progresses at a more rapid rate in the younger diabetic patient.

PATHOPHYSIOLOGY

Type 1 diabetes appears to be caused by an inability of the pancreas to secrete adequate insulin to meet the metabolic demands of the body. As this process unfolds, the progressive destruction of β -cells leads to a progressive deficiency of insulin, one of the body's major anabolic hormones, with approximately 90% of the functional β -cell mass needing to be destroyed before blatant glucose intolerance occurs.⁵ Hence, the results of cell destruction may take months or years to manifest.

In the normal metabolic state, there are regular swings between the high-insulin anabolic state immediately following the ingestion of a meal and the low-insulin, fasting, catabolic state. This stimulates energy storage for immediate or future use in the form of glycogen, protein, and adipose tissue. However, with Type 1 diabetes, this lack of insulin leads to decreased entry of glucose into cells resulting in the mobilization of stored substrates. Lipolysis, glycogenolysis, and proteolysis are utilized for energy in the absence of adequate glucose in the cells. Fat breakdown causes increases in serum cholesterol, free fatty acids, and triglycerides, while the over-utilization of protein for cell energy creates the catabolic state. Therefore, patients with Type 1 diabetes are always in the chronic low-insulin, catabolic state.⁷

In addition to insulin deficiency, increased plasma concentrations of counter-regulatory hormones further compound the metabolic disturbances. Epinephrine, cortisol, growth hormone, and glucagon accelerate and exaggerate the rate of metabolic decompensation. The mechanisms by which these hormones exert this effect include impairment of insulin secretion and antagonizing insulin action. They also promote glycogenolysis, gluconeogenesis, lipolysis and ketogenesis while decreasing glucose utilization and glucose clearance.⁷

CLINICAL MANIFESTATIONS

The most common clinical manifestations of Type 1 diabetes include a history significant for polyuria, polydipsia, polyphagia, and weight loss.⁸ With progressive insulin deficiency, excess glucose production and its impaired utilization result in hyperglycemia and subsequent glycosuria when the renal threshold of 180 mg/dL of glucose is exceeded.⁸ Glycosuria increases the osmotic load of the urine producing polyuria, excess electrolyte wasting, dehydration, and polydipsia in an attempt to compensate for the loss.⁸ A feeling of hunger is triggered when the body's is not ability to transport glucose into cells. In response to this feeling an individual may eat and thereby increase their caloric intake.⁸ Additional symptoms include lethargy, weakness, pyogenic skin infections, dry skin, and, in females, monilial vaginitis. The duration of these symptoms varies among patients but is often less than one month.⁸

If the diagnosis of Type 1 diabetes is not made and treatment is delayed, further decompensation will occur, ultimately resulting in DKA. A stressful event (e.g., acute infection) generally precipitates DKA and is responsible for the initial presentation in many diabetic children. Early manifestations in mild cases of DKA include vomiting, polyuria, and dehydration. In the more severe circumstances, Kussmaul respirations ("sweet" smelling breath due to acetone), and abdominal pain and rigidity, which frequently disappears after several hours of fluid, electrolyte and insulin therapy, may also be present.² Laboratory findings include hyperglycemia, ketonemia, glycosuria, ketonuria, metabolic acidosis, hyponatremia and hypokalemia.²

Once the stressful event that initially precipitates the diabetes is resolved, the majority of newly diagnosed children undergo a remission or "honeymoon" phase.⁹ During this phase, which may last up to 1 year, the remaining pancreatic β -cells produce enough insulin to meet some or all of the patient's metabolic needs. Exogenous insulin requirements often decrease to <0.5 units/kg/d, while some patients require no insulin administration during this period.

It is important to educate both the patient and family that, despite this temporary return to metabolic normalcy, the insulin deficiency associated with Type 1 diabetes soon recurs. To avoid

the misinterpretation of this phase as a cure, many physicians will maintain patients on low dose insulin therapy and continue to monitor hemoglobin A₁C (HbA₁C) levels during this period.⁹

DIAGNOSTIC CRITERIA

Children in whom diabetes is suspected may be divided into three categories: 1) those with a history consistent with diabetes (i.e., polyuria, polydipsia, failure to gain weight, weight loss, enuresis, lethargy, or fatigue); 2) those with transient or persistent glycosuria; and 3) those with DKA with or without coma. In all circumstances, diagnosis is dependent on the presence of hyperglycemia in association with glycosuria with or without ketonuria, when there is no evidence of other metabolic disorders that interfere with carbohydrate metabolism. The presence of classic symptoms in conjunction with a random plasma glucose concentration of ≥ 200 mg/dL or a fasting plasma glucose (FPG) concentration of ≥ 126 mg/dL is considered diagnostic for Type 1 diabetes. Confirmation that the diabetes is Type 1 requires measurement of islet cell autoantibodies or autoantibodies to insulin.¹ Elevated cost and lack of easy access make the oral glucose

tolerance test a rarely used diagnostic procedure for the pediatric patient. HbA₁C measurement is not currently recommended for the diagnosis of Type 1 diabetes.¹ However, HbA₁C, along with FPG concentrations, are the measurements of choice in monitoring the subsequent treatment of diabetes.¹

MANAGEMENT

Insulin Therapy

The goals of management for the patient with Type 1 diabetes are to achieve normal growth, reduce the episodes of hyper- and hypoglycemia, and lessen the risk of long-term complications. The methods by which these goals are attained include delivery of insulin in sufficient quantities to meet metabolic needs, monitoring of blood glucose concentrations, devising and maintaining appropriate nutritional plans, and getting adequate exercise. The initial management of the newly diagnosed child with Type 1 diabetes often requires short-term hospitalization for the treatment of DKA. This consists of fluid and electrolyte management, intravenous insulin and glucose administration and intense monitoring of blood glucose levels. During this hospital admission, the patient must be educated on

Table 1. Insulin pharmacokinetics^{8,12, 32}

Type of Insulin	Source	Onset (hrs)	Peak (hrs)	Duration (hrs)
Regular (Humulin R, Novolin R, Velosulin BR, Iletin II Regular)	Human and pork	0.5–1	1–5	8–12
Lispro (Humalog)	Human	0.25–0.5	0.5–1.5	6–8
NPH (Humulin N, Novolin N, NPH Iletin II, NPH)	Human and pork	1–4	4–14	14–24
Lente (Humulin L, Novolin L, Lente Iletin II)	Human and pork	1–4	4–14	16–24
Ultralente (Humulin U)	Human	4–10	12–20	20–36
Humulin 70/30 Novolin 70/30	Human	0.5	4–8	24
Humulin 50/50 Humalog 50/50	Human	0.5–1	2–12	Up to 24
Humalog 75/25	Human	0.25	0.5–1.5	Up to 24
Insulin glargine (Lantus)	Human	--	--	24

insulin administration; blood glucose monitoring; the signs, symptoms and treatment of hypo- and hyper-glycemia; and initial nutritional interventions.¹⁰

Once the patient is stabilized, subcutaneous insulin therapy is initiated based on the previous 24-hour intravenous requirements, with the average daily replacement dose being 0.7–1.2 IU/kg/d.^{1,10,11} Several factors influence the required daily insulin dose. Meals may change in composition, timing, and size, especially in small children where meal planning is difficult. The amount of physical activity varies according to patient age, with most small children being unpredictable. Adolescent and obese patients, who are often insulin resistant, may require up to 1.3 IU/kg/d due to insulin resistance, while children <5 years of age may require as little as 0.5 IU/kg/d due to insulin sensitivity.^{1,10,11} Psychological stress, infections, and fever increase in counter-regulatory hormone secretion and thus increase the need for insulin.

An important exception occurs during the honeymoon period when insulin requirements may drop below 0.5 IU/kg/d.^{1,10,11} A number of insulin preparations with different onsets and durations of activity are currently available (Table 1). Purified pork and human insulin are the insulin preparations most commonly used in children. Although standard beef and pork mixtures are still available, their use is discouraged in the pediatric population because of the increased antigenicity associated with the beef component in comparison to pork or human insulin. Human insulin has a more rapid onset and duration of action and is less antigenic when compared to pork insulin.¹²

Regular insulin is a short-acting insulin with an onset of action of 50–60 minutes.⁸ It is a clear, colorless solution that can be administered by the intravenous, intramuscular, or subcutaneous route. Insulin lispro (Humalog) and human insulin aspart (NovoLog) are rapid acting insulin analogs, with an onset of action of 15–30 minutes.⁸ This rapid onset allows these agents to be injected immediately before eating, instead of the required 20–45 minutes prior to eating as is required for regular insulin. Like regular insulin, they are also clear, colorless solutions that can be administered by intravenous, intramuscular, or subcutaneous routes. This is in direct contrast to all other insulin products, which are suspen-

sions. These suspensions contain either protamine or zinc and must be administered subcutaneously.¹²

NPH and Lente insulins are “intermediate-acting” due to their longer duration of action (approximately 14–24 hours).⁸ They are similar in their onset, peak, and duration of activity; however, they differ in their ability to be mixed with regular insulin. NPH can be mixed in a syringe with regular insulin, insulin lispro, or human insulin aspart and refrigerated for up to 21 days without losing potency.⁸ In contrast, when Lente insulin and short-acting insulins are combined in a syringe, the zinc found in Lente insulin binds with the short-acting insulins within 15 minutes and decreases the amount of insulin by producing more Lente insulin.⁸ If used in combination, patients should inject the mixture immediately after filling the syringe or consistently wait 24 hours before administration of the contents.⁸ Premixed combinations of human regular and insulin lispro with NPH insulin are available but are not routinely used in pediatric patients because of the lack of flexibility in dosing.¹²

Ultralente, a long acting insulin with a duration of action of approximately 24–36 hours, may also be used as a single or twice-daily dosing regimen to provide continuous control throughout the day with regular insulin given before each meal.¹² For patients who are highly motivated, continuous subcutaneous insulin infusion pumps with regular insulin can be used. This may be difficult to arrange in the school age child without interfering with their school schedule.

“Novel Insulin Systems.”

Investigators are currently developing new insulin preparations, including many different insulin analog products such as insulin glargine (Lantus). This is a long-acting, relatively peakless insulin analog that allows once-daily dosing as a patient’s basal insulin. In addition to new injectable forms of insulin, researchers continue to investigate and refine insulin products that may be administered via other routes other than injection (i.e., intranasal and oral). Together, these ongoing advances promise to provide new and improved methods for the management of Type 1 diabetes in the near future.

A variety of strategies can be used to tailor the insulin regimen to the individual lifestyles

of pediatric patients and their families. Conventional insulin therapy with two daily injections of insulin is still the most common regimen used in the pediatric patient. This consists of the administration of split-mixed intermediate and regular insulin in a 2:3 (regular:intermediate) ratio with two-thirds the daily dose given before breakfast and one-third given before dinner. This regimen is most practical in the very young child who fights each injection, children who are at school during lunch and may be too young to administer their own insulin, and in patients who are unable to sustain a strict 3 to 4 daily injection schedule. However, adequate control between dinner and breakfast may not be possible with pre-dinner administration of NPH insulin due to the shorter time to peak concentration and duration of action seen with the intermediate human insulins.¹³

If the patient experiences morning hyperglycemia or nocturnal hypoglycemia, the preferred approach to evening insulin administration is to administer the dose of regular insulin prior to dinner and move the intermediate insulin dose to bedtime.¹³ The three daily injections cause a peak of insulin activity in the early morning hours, reducing the risk of hypoglycemia during the night and producing better blood glucose control in the morning. It also gives more flexibility at dinner and for sports activities held after dinner.

Adjustments in the intermediate-acting insulin should only be made every 2–3 days based on the child's blood glucose patterns. Regular, lispro, or aspart insulin can be adjusted with each dose based on the blood glucose and anticipated food intake. A change of 1–5 units of the short-acting insulin is usually sufficient to accommodate these changes. In children with inadequate glucose control in the afternoon, the addition of short-acting insulin prior to lunch or an afternoon snack may be appropriate.¹³

There is much controversy over the benefit versus risk associated with intensive diabetes management and the appropriate target blood glucose concentrations in the various pediatric age groups. The controversy centers around the prevention and delay of long-term complications associated with diabetes and the risk of developing severe hypoglycemia in young children during intensive insulin therapy. The Diabetes Control and Complications Trial (DCCT) was the

first large scale, clinical trial to compare intensive versus conventional insulin therapy in the prevention and delay of early microvascular and neurologic complications associated with Type 1 diabetes.³ In addition to other age groups, this study enrolled and followed 195 pubertal, adolescent patients for a mean of 7.4 years. An important difference noted between adolescents and adults was the adolescents' ability to achieve and maintain HbA_{1c} concentrations in the non-diabetic reference range (4%–6%), with the mean values in intensely treated adolescents being statistically higher than those observed in intensely managed adults, 8.1% vs. 7.1%, respectively.

These higher HbA_{1c} values were seen in adolescents despite a larger daily dosage of insulin. There was also an increase in HbA_{1c} values in adolescent patients treated with conventional insulin therapy when compared to adults, 9.8% vs. 9% respectively. This suggests that this age group is the most difficult to manage. However, further analysis of the relationship between overall glycemic control and the risk of complications suggest that even a modest decrease in HbA_{1c} (i.e., 10%) is of direct and substantial benefit to the patient. Based on this information and the lack of evidence to suggest that conventional protocols protect against hypoglycemia, intensive regimens should be advocated for pediatric patients based on the individual and family capabilities rather than age criteria.^{3,14,15}

Patients and parents should be given age-related target guidelines for glycemic control. The suggested preprandial goal for children over 5 years of age is a blood glucose concentration of 70–150 mg/dL and a 1-hour postprandial value no greater than 180–200 mg/dL.¹ These goals are modified for patients under the age of 5 due to the increased concern over the severe consequences of hypoglycemic episodes on brain development. In this population, preprandial blood glucose values of 100–200 mg/dL are acceptable.¹ In young infants and toddlers, most values, with the exception of the first morning concentration, are postprandial because of the increased frequency in food consumption. In these patients, HbA_{1c} may be more indicative of the quality of glycemic control.¹⁶

Monitoring

The cornerstone of management in the patient with Type 1 diabetes is self-monitoring of

blood glucose. Patients should take frequent blood glucose measurements to adjust premeal insulin doses and monitor the effectiveness of intermediate or long acting insulin therapy. This consists of checking finger stick blood glucose concentrations four times daily - before breakfast, lunch, dinner, and bedtime. In addition, patients should periodically measure 3:00 am blood glucose levels to adjust overnight insulin

replacement. Younger patients routinely have difficulty recognizing the symptoms of hypoglycemia, necessitating additional finger sticks. Patients should be advised to avoid overly aggressive premeal and bedtime insulin supplements. During times of illness, more frequent monitoring is necessary.¹⁰

Numerous reagent strips, glucose meters, and finger puncture devices are available to fa-

Table 2. Glucometers, Lancets, and Devices Currently Available¹²

Glucose Meters	Lancet Devices	Lancets
<i>Bayer</i> Glucometer Dex, Glucometer Elite, Glucometer Elite XL, Glucometer Encore	<i>Bayer</i> Ames Glucolet Automatic Lancing Device, Microlet Automatic Lancing Device, Microlet Vaculance	<i>Bayer</i> Ames Gluco System Lancet, Microlet Lancet
<i>Boehringer Mannheim</i> Accu-Check Advantage, Accu-Check Complete, Accu-Check Easy, Accu-Check Instant, Accu-Check Instant DM, Accu-Check Simplicity	<i>Becton Dickinson</i> B-D Lancet Device	<i>Becton Dickinson</i> B-D Ultra-Fine II Lancet
<i>Cascade Medical</i> Checkmate Plus ChronimedAssure, Select GT, Supreme II	<i>Can-Am Care</i> Monojector Lancet Device ChronimedSelect Lite Lancet Device, Lasette Laser Lancing Device	<i>Can-Am Care</i> E-Z Ject Lancet, Monolet Lancet
<i>HDI (Home Diagnostics, Inc.)</i> Diascan Partner, Prestige, Prestige IQ, Prestige LX	<i>HDI</i> Dialet II	<i>Chronimed</i> Haemolance, Techlite Lancet
<i>MediSense</i> ExacTech, ExacTech RSG, Precision QID, Precision QID Pen	<i>LifeScan, Inc.</i> Penlet Plus Adjustable Blood Sampler, Penlet Plus Adjustable Blood Sampler	<i>Gainor Medical</i> Cleanlet, Surelite Lancet
	<i>Medicore Inc.</i> Lite Touch Lancing Device	<i>ITC</i> Tenderlett ITC
	<i>Medisense Inc.</i> Ultra TLC	<i>Lifescan Inc.</i> LifeScan Lancet, One Touch Finepoint Lancet
	<i>Owen Mumford</i> Autolet Lite, Autolet Mini	<i>Medical Plastic Devices</i> Vitalet Lancet
	<i>Palco Laboratories</i> Auto-Lancet	<i>Medicore Inc.</i> Lady Lite Lancet, Lite Touch Lancet
	<i>Roche Diagnostics</i> Accu-Check SoftClix Lancet Device, Accu-Check Soft Touch Lancet Device	<i>Medisense</i> Ultra TLC
		<i>Owen Mumford</i> Unilet GP 28 Lancet, Unilet GP Superlite Lancet, Unilet GP Lancet, Unilet Lancet, Unilet Comfort Touch, Unistik 1, Unistik 2
		<i>Palco Laboratories</i> EZ-Lets, EZ-Lets Thin, EZ-Lets II
		<i>Roche Diagnostics</i> Accu-Check Softclix Lancet, Accu-Check Soft Touch Lancet, Safe-T Pro
		<i>Ulster Medical</i> Gentle-Let Lancets, GP, Gentle-Let Lancets, Safety, Gentle-Let 1

cilitate frequent, accurate monitoring. These devices are small, portable, and accurate, with the ability to store 250–300 readings with the date and time in the memory. A listing of the available devices can be found in Table 2. As with all home-monitoring kits, product choice will depend on patient and insurance preference, as well as cost of the machine and test strips.¹⁰

The best measurement of chronic glucose control is HbA_{1c}. This is an objective level that represents an average blood glucose reading over the previous 3 months, with 50% of the result dependent on the immediate past 30 days, 25% from 30 days prior to that, and 25% from two months prior.¹⁶ These concentrations should be monitored every 3–6 months. A HbA_{1c} of 7% equals approximately 150 mg/dL. In general, every HbA_{1c} percentage point above 7% is equivalent to a mean change in blood glucose of 30 mg/dL after 150 mg/dL.^{15,16} For example, a HbA_{1c} of 12% is equal to 300 mg/dL. Various normal ranges exist; however, the upper limit is generally 6.9%. Many patients will be able to achieve non-diabetic values of <7%, but a number of patients may not achieve concentrations within the goal range. While guidelines must be individualized, every attempt should be made to achieve the lowest possible HbA_{1c} value without inducing hypoglycemia. According to the DCCT, any improvement in glycemic control, even at concentrations >8%, is associated with a reduction in the risk of developing long-term complications, such as retinopathy, microalbuminuria, and neuropathy.^{15,16}

Diet and Exercise

Nutritional counseling should be initiated within the first few days of insulin therapy. An initial daily calorie intake should be defined based on age; intake = 1,000 kcal/d + 100 kcal/d X (age in years up to 12 years of age).¹⁷ This daily calorie intake should be further adjusted based on eating patterns and preferences, family need, cultural practices, and special needs of the patient. The American Diabetes Association (ADA) recommends a carbohydrate intake up to 55%–60% of total energy, in the form of complex carbohydrates.^{16–18} Current recommendations for protein intake are 15%–20% of energy.^{16–18} Often this is less than what the patient has been consuming. Finally, the ADA recommends <30% of total energy from fat, with <10% saturated fat,

6%–8% polyunsaturated fat, the remainder monounsaturated fat, and <300 mg of cholesterol daily.^{16–8} All children should receive three meals, with optional late afternoon and prebedtime snacks, with a goal of consuming all calories at nearly the same time daily.^{16,18}

Exercise is an important tool in the management of diabetes. It improves insulin sensitivity and lipoprotein profile, maintains body weight, and decreases blood pressure. Since hypoglycemia is most likely to occur during times of peak insulin activity (e.g., during exercise, extra calories), lower insulin doses may be needed during these periods. Regular exercise should be encouraged for children of all ages and integrated into the child's health care regimen, with appropriate counseling on increasing calories, decreasing insulin, or both to maintain acceptable glucose concentrations throughout the exercise period. It is equally important that these children have a source of calories readily available during physical activity and while they are driving. Medical alert bracelets or necklaces should also be worn at all times.¹⁶

CARBOHYDRATE COUNTING

In an ideal treatment plan for a patient with Type 1 diabetes, the patient must count the carbohydrate content of their meals to determine their intermittent insulin needs. Carbohydrates account for most of the glucose that is in the bloodstream immediately after meals. Almost all (90% to 100%) of the digestive starches and sugars consumed convert to blood glucose within 20 to 90 minutes.¹⁹ In contrast, only about half of the protein and even less of the fat we eat are eventually converted to glucose.¹⁹ With training in carbohydrate counting, many patients with Type 1 Diabetes can determine the correct bolus dose for any meal or snack by counting or estimating the carbohydrate content.

Every person has a unique ratio of the number of grams of carbohydrates consumed and the number of units of insulin that the body requires to utilize them. The insulin sensitivity factor, or insulin-to-carbohydrate ratio, is what patients use to calculate the appropriate intermittent insulin dose before a meal or snack. The insulin to carbohydrate ratio may vary from one unit of insulin for every 10 to 15 grams of carbohydrates in adults. In children, this ratio varies from 15 to 20

grams of carbohydrate for every unit of insulin. In addition, the more a person weighs, the less effective 1 unit of insulin becomes.¹⁹ The insulin-to-carbohydrate ratio can range anywhere from 1:16 for people weighing 45–50 kg to 1:6 for people weighing over 109 kg.

Although counting carbohydrates takes a great deal of time and effort to learn, it allows more flexibility in meal planning. Unfortunately, it sometimes gives patients the impression that they can eat “whatever they want whenever they want it.” Patients who ascribe to this belief often experience obesity, elevated blood lipid concentrations, and hypertension. Adjusting intermittent insulin based on insulin to carbohydrate ratios should be undertaken with the supervision of a physician, pharmacist, or dietician trained in the carbohydrate counting technique.

MANAGEMENT OF HYPOGLYCEMIA

The DCCT has shown that with better blood glucose control there is an increased incidence of hypoglycemia. For this reason, it is important to educate all patients, family members, and teachers associated with a child with insulin-dependent diabetes on the signs and symptoms of hypoglycemia and its proper management. Patients who may be at a high risk for the development of hypoglycemia include the following: patients with a prior history of severe hypoglycemia, a lower HbA_{1c} value, increased duration of diabetes, lower endogenous insulin secretion, elevated HbA_{1c} before initiation of therapy, and larger insulin dose per kilogram of body weight.¹⁰ Males and adolescents also may be at high risk for hypoglycemia.¹⁰

Children with hypoglycemia should be treated promptly, ingesting 10g to 15 g of simple sugars (i.e., 3 glucose tablets, 1-half cup of fruit juice, 5–6 pieces of hard candy). Once the hypoglycemic episode has been treated, the patient should be instructed to wait 15 to 20 minutes and test the blood again. If the blood glucose is still low and symptoms do not resolve, treatment should be repeated. After the hypoglycemic episode subsides, patients may eat regular meals and snacks as planned to keep their blood glucose in the recommended reference range. It is important to treat hypoglycemia quickly because it may progress to the point of unconsciousness. If syncope is noted, hypoglycemia should be con-

firmed with a finger stick, and immediate treatment with an injection of glucagon should be given. Patients should then be taken directly to the emergency department for inpatient treatment.¹⁷

TRADITIONAL INSULIN ADMINISTRATION SYSTEMS

Traditionally, insulin has been administered intermittently via an insulin syringe. In the recent past, diabetes research has focused on developing more convenient insulin delivery systems in a hope to increase compliance with insulin therapy and improve the management of Type 1 diabetes in both children and adults.

Insulin Jet Injectors

The insulin jet injector is a needleless system that sends a fine spray of insulin through the skin by a high-pressure air mechanism. The jet injector is usually preferred in the subset of patients who suffer from phobias associated with needles. However, these devices have found limited use because of their expense (several hundred dollars) and size of approximately 8 oz. An advantage of this system versus other ones mentioned is that absorption of regular human insulin is more rapid than from an injection into subcutaneous sites.²⁰ Disadvantages with these devices include the potential for a decreased amount of absorbed insulin and pain or bruising at the injection site if the injector is not adjusted correctly.²⁰

Insulin Pen

Medical therapy for diabetes has changed dramatically since the discovery of insulin in 1921.²¹ Not only have therapies for diabetes advanced significantly, but the traditional method of administering insulin with a needle and syringe has also been simplified into a newer insulin pen injection system. This system resembles an everyday pen with a cartridge that contains a fine, short needle on the tip of the pen. Users turn a dial to select the desired dose and press a plunger on the end to deliver the insulin just under the skin. Insulin pens provide a quick and easy method for insulin administration. However, their biggest drawback is the inability to mix two types of insulin together to allow one injection, as is often possible with the traditional

insulin syringe. Therefore, in situations where more than one type of insulin needs to be administered, patients must often use two different insulin pens to accommodate their insulin regimen.²²

At this time; two types of insulin pens are available in the United States, the pre-filled pen and the reusable pen. Pre-filled pens are discarded after use while reusable pens have a replaceable cartridge that is loaded into the pen by the patient. Currently, regular human insulin, human isophane insulin, 70% human isophane insulin suspension with 30% regular human insulin and insulin lispro are all available in pen injection systems.

Newer therapy includes 75% insulin lispro protamine suspension with 25% insulin lispro and 50% insulin lispro protamine suspension and 50% insulin lispro. Care must be taken to assure that the correct refill cartridge is obtained for the patient's pen device, as pen and cartridge configurations vary and are not all interchangeable. For pediatric patients, Becton Dickinson's B-D Pen Classic and B-D Pen Mini are available as pediatric "POP" pens, which are available in various bright colors and patterns to help young children differentiate between pens that contain rapid-acting insulin and those that contain intermediate-acting insulin preparations.²¹

The use of the insulin pen is similar regardless of whether a pre-filled pen or a reusable pen is selected. Cartridges should be kept in the refrigerator until they are placed into a refillable pen; afterwards, the insulin pen may remain at room temperature for up to one month.²¹ Upon use of the insulin pen, patients must possess adequate manual dexterity and visual acuity to attach and detach a needle for each injection.²⁰ When injecting the insulin, the needle should remain in the subcutaneous tissue for 5 seconds after the plunger has been completely depressed.²¹ Newer pens are available with larger, easy-to-read numbers or an audible click as the dose is dialed or when the plunger is depressed.²⁰

Insulin pen devices have important advantages over conventional insulin syringe dosing. More convenient insulin delivery, increased dosing accuracy, decreased pain at injection site due to overused the use of smaller needles, and improved quality of life have been noted with the use of the pen delivery system. Insulin pens may also provide the patient with more flexibility in

their management, leading to improved patient compliance. Disadvantages of insulin pens include the potential of loss of sterility when patients employ reusable pens. Also, damage may occur to the pen device over time.^{20,21} Estimates show that only 2% of all insulin is administered via insulin pen in the United States, whereas other countries use insulin pens at rates between 70% - 90%. Low usage rates may be due to reimbursement difficulties with insurance companies, or they may result from a simple lack of patient and physician knowledge about pen availability.²¹

The department of pediatric endocrinology at the Mayo Clinic in Rochester, Minnesota, compared the accuracy and precision of insulin syringes and pen devices when used in pediatric patients with Type I diabetes.²³ Thirty-two pediatric patients and 16 additional adult caregivers of other pediatric patients were instructed to measure out the child's normal morning insulin dose using 2 radio labeled solutions representing regular insulin and NPH insulin. Twenty-four children (mean age of 14.1 years) had previous experience with using both conventional insulin syringes and pen injector devices. For insulin doses ≤ 5 IU, these patients had a decreased absolute error in measuring out regular insulin doses via pen devices when compared to insulin syringes ($P < 0.01$). However, when the same comparison was made for insulin doses > 5 IU, no significant differences in absolute error were seen. This study concluded that insulin pen devices may provide an advantage in accuracy over traditional syringe dosing when measuring insulin doses ≤ 5 IU.²³

Insulin Pumps

Continuous subcutaneous insulin infusion (CSII) with a portable pump can be used to provide tight insulin control for insulin-dependent diabetics while providing increased flexibility. In addition, the pump can bring blood glucose concentrations closer to normal, decrease blood glucose swings, and reduce or eliminate nighttime lows and morning highs. CSII, using regular or lispro insulin, provides a constant amount of insulin throughout the day and night. Portable insulin pumps not only provide a preprogrammed basal rate, but they can superimpose pre-meal intermittent doses of insulin, which may be varied according to ambient blood

sugars, carbohydrate content of meals, or exercise.²² Therefore, frequent blood glucose monitoring is essential to determine insulin dosages and to insure that insulin is delivered.

The external insulin pump is a mechanical device that is battery-powered and operated by a computer chip. The computerized device holds a syringe containing a two- to three-day supply of regular insulin or lispro insulin. A small catheter attaches the reservoir to an indwelling subcutaneous catheter or needle that is changed every two or three days. Infusion rates are controlled by a microprocessor that the user programs for basal rates and intermittent doses.¹⁰ Recent advances in the design of the pump have made both the catheters and needles available in multiple lengths and angles. With current pumps, patients have the ability to disconnect the infusion set and pump while leaving the catheter in place.

Patients can then spend limited amounts of time away from the pump, without the need to re-insert a needle or catheter when they re-connect.²⁴ In addition, many patients prefer newer infusion sets that allow them to place the catheter subcutaneously with an introducer needle and then remove the needle, leaving only the catheter in place. Most pump users choose the abdomen as their site of infusion because insulin absorption is most consistent from this site, and it is a comfortable place to wear the pump; however, any area with adequate subcutaneous tissue is acceptable, including the thigh, hip, and buttock.²⁵

Many believe CSII to have important advantages over traditional injection therapy. By using only fast-acting insulin, patients may see a more consistent and predictable insulin effect than seen with longer-acting insulin. In addition, the patient's basal rate is easily adjusted with CSII in response to changes in basal requirements throughout the day or in response to different levels of physical activity.¹⁰ Many patients enjoy the extreme lifestyle flexibility that CSII therapy has to offer. With CSII therapy, patients are not limited to eating a certain amount of food at a set time because they have taken a dose of intermediate-acting insulin several hours prior. Moreover, patients can maintain a steady blood glucose concentration while sleeping without worrying that it will fall too low because of an insulin peak in the middle of the night. Disad-

vantages of CSII include the following: a greater cost than traditional injection therapy, a potential risk of infection at the infusion site, as well as potential damage to the pump or interruption of therapy when the pump is disconnected during contact sports.¹⁰

The American Diabetes Association has published criteria that they feel patients must meet to benefit from CSII.²⁴ These criteria include the ability to care for and operate the pump independently, possessing good judgment and problem-solving skills, motivation, willingness to work with the health care team, and the ability to learn how to deal with the data effectively to translate it into programming for the pump. Unfortunately, CSII criteria are not specific for pediatric patients. Besides the obvious need for pediatric patients to regularly monitor their blood glucose, they must also be able to independently manage their diabetes while away from their parents (e.g., at school). To accomplish this, ideally, pediatric patients should be able to adjust insulin intermittent doses based on the carbohydrate content of the meal, the blood glucose concentration before the meal, and what activities are planned post-prandially. Some experts say that select children between 8 and 10 years of age may be able to perform these activities; however, most children 10 to 12 years of age should be able to manage CSII therapy. Regardless of insulin administration method, experts agree that continued parental involvement throughout adolescence results in better diabetes management.²⁴

Many studies have been published on the use of CSII in adults, but few have looked at the use of CSII in pediatric patients. The Division of Endocrinology and Metabolism at Children's Hospital in Los Angeles has published their experiences using CSII therapy in 83 pediatric patients.^{24,25} Patients in the study had a mean age of 13.6 ± 3.9 years when they began to use their pumps and had a mean duration of diabetes diagnosis of 5.3 ± 3.2 years. In this study, 37% of patients were described as unmotivated and having poor diabetic control, 6% had severe hypoglycemia, 15% were started on CSII therapy only at night through a research protocol, and the remaining 42% were highly motivated and started CSII to improve their diabetic control or address a diabetes management problem. At the end of the 5-year study period, significant increases

were seen in scores on tests of knowledge, adherence, responsibility, guidance and control, integration, and quality of life. CSII therapy also resulted in an approximately 20% reduction in insulin dosage. No change in body mass index or HbA_{1c} was seen. Ninety percent of patients reported in the study chose to continue CSII therapy.^{24,25} Additionally, Yale Children's Clinical Research Center published the results of a 12-month study comparing the use of CSII with multiple daily injections in adolescent patients with type 1 diabetes.²⁶ One-third of the adolescents chose to receive the CSII therapy. At the end of the study period, adolescents in the CSII group had lower HbA_{1c} concentrations and 50% fewer hypoglycemic events.²⁶ Although limited in number, the published clinical trials evaluating CSII therapy in pediatric patients have shown success.

NOVEL INSULIN DELIVERY

New approaches to insulin delivery for Type 1 diabetes continue to be developed at a rapid rate. Implantable insulin infusion pumps, sometimes referred to as the "artificial pancreas," continue to be studied in numerous clinical trials. These insulin pumps are surgically implanted, usually on the left side of the abdomen. The relatively small, lightweight devices are designed to contain several weeks' supply of insulin and to have a battery life of several years. The pump delivers a basal dose of insulin continuously, and dose adjustments are accomplished via a radio controller.²⁰ An advantage of this method is that, like insulin produced naturally from the pancreas, the insulin from the implantable pump goes directly to the liver to prevent excess hepatic glucose production. However, the leading obstacles to this form of insulin delivery continue to be foreign body tissue reaction, catheter blockage, insulin stability, and cost.²⁷ When these obstacles are encountered, additional costs are often incurred due to catheter or insulin replacement, or CSII therapy is discontinued.

Inhaled Insulin

The concept of administering insulin via an inhaled route is an appealing one for diabetic patients since this would potentially eliminate the need to administer insulin in any system that uses needles. Current inhaled insulin delivery systems provide insulin as a dry powder or solu-

bilized insulin formulation that is inhaled through the mouth directly into the lungs. Once in the lungs, the alveoli provide a well-vascularized area for the distribution of insulin into the bloodstream. Initial studies researching inhaled insulin have shown a hypoglycemic effect from this route of administration; however, issues surrounding reliability and bioavailability remain.²⁷ Bioavailability in Type 2 diabetics and in healthy volunteers has been shown to be approximately 20% although studies in Type 1 diabetics have not been published.²⁸ Nonetheless, there are many technical aspects of inhaled insulin administration that must be addressed.²² Current research is centering on the development of better inhaler systems for insulin delivery that would allow more precise insulin dosing.^{27,28}

Insulin Patches

Transdermal insulin patches are also being studied as a method of insulin delivery. Once placed on the skin, the patches use a process called iontophoresis which uses electrical currents to move large, charged molecules like insulin from the patch across the skin. The insulin patch would provide a continuous low dose of insulin. To administer insulin bolus doses before meals, users would pull off a tab on the patch to release additional insulin. The development process of this delivery system has revealed that insulin does not penetrate skin as easily as other molecules that are commonly administered by transdermal patches.²⁰ Currently, no published animal studies compare transdermal insulin to traditional subcutaneous dosing.

Nasal Insulin

Nasal delivery of insulin has been investigated for many years and remains a feasible option for insulin delivery. The main advantages of this method are ease of delivery, fast absorption time (15 minutes), and good biologic activity.²⁹ Plasma glucose has been shown to be lowered by 50% in 45 minutes in fasting normal controls and in 120 minutes in fasting Type 1 diabetics.²⁹ HbA_{1c} results have shown statistically insignificant differences when compared to traditional subcutaneous dosing.³⁰ Unfortunately, most experts view the nasal route as an impractical route for insulin delivery due to nasal irritation it may cause, which varies proportionally

to surfactant concentration²⁹ and specific absorption enhancer used.³⁰

Oral Insulin

Oral insulin has not proved promising for the treatment of insulin-dependent diabetes. Current technology has been unable to overcome the digestive processes in the stomach that inactivate the peptide. At this time, oral insulin may not be feasible for the treatment of diabetes; however, its use is being investigated as an agent that alters the immune process in individuals at high risk to develop insulin-dependent diabetes.²² High risk individuals include people who have relatives with Type 1 diabetes and high concentrations of islet cell antibodies.²² This approach is currently being investigated in children and adults in the American Diabetes Prevention Trial-Type 1.^{22, 31}

SUMMARY

Type 1 diabetes is a disease that is associated with many risk factors and the development of long-term complications. Recently, patients with Type 1 diabetes have increased options through the addition of insulin lispro, insulin glargine, and CSII. With these advances in therapy, pediatric patients with Type 1 diabetes have been able to achieve strict glycemic control, although the treatment of hypoglycemia remains a burden. Advances in technology and drug therapy are occurring at a rapid pace with transplantation of islet cells and a vaccine for diabetes mellitus being two exciting areas of research. As healthcare practitioners caring for pediatric patients with Type 1 diabetes, our ultimate hope is that in the near future, a cure will be found, and diabetes mellitus will be a disease of the past.

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