New Steps in Treatment of Type 1 Diabetes Mellitus

Done By: Namareq Mahdi Jassim
Supervised by: Dr. Hailah Othman Habeeb/ lectural doctor /M.B.Ch.B –F.I.C.MS/P/Department of pediatrics
University of Diyala /College of Medicine

ABSTRACT: Type 1 diabetes mellitus also known as autoimmune diabetes is a chronic disease characterized by insulin deficiency due to pancreatic β-cell loss and leads to hyperglycemia. Mostly symptoms occur during childhood or adolescence but can sometimes develop later. The risk of developing long-term complications of type 1 diabetes (T1D) is related to glycemic control and is reduced by the use of intensive insulin treatment regimens: multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII). Majority of the patients and families chose to continue with CSII after the completion of the studies, even in studies where insulin pumps showed no objective benefit.

KEYWORDS: Diabetes Mellitus [DM], Multiple Daily injections [MDI], Continuous subcutaneous insulin infusion [CSII]

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disorder of glucose homeostasis characterized by autoimmune destruction of the insulin-producing pancreatic b-cell that progressively leads to insulin deficiency and resultant hyperglycemia. If left un-treated, insulin deficiency leads to progressive metabolic derangement, with worsening hyperglycemia, ketoacidosis, starvation, and death. [(1)] In an effort to restore and maintain euglycemia, treatment attempts to mimic the action of the native b-cell by exogenously replacing insulin and includes frequent monitoring of blood glucose levels. As the visionary pioneer Dr. Elliott P. Joslin believed, the best possible outcomes of T1DM treatment are realized when a sense of empowerment, rather than victimization, is imparted to both patient and family. Achieving this empowerment through diligence and education enables an individual living with T1DM to attain optimal health and well-being and constitutes the ultimate goal and challenge of the medical team. The epidemiology and pathophysiology of T1DM are discussed in this article, followed by a practical review of the diagnosis and treatment of this chronic, lifelong condition emphasizing the goal of effective diabetes self-management as leading towards enduring wellness. [(2)] Individual risk factors can have separate pathophysiological processes to, in turn, cause this beta cell destruction. Still, a process that appears to be common to most risk factors is a type IV hypersensitivity autoimmune response towards beta cells, involving an expansion of autoreactive CD4+ T helper cells and CD8+ T cells, autoantibody-producing B cells and activation of the innate immune system. [(3)]

A predisposition for T1DM begins at birth with the in-heritance of genetic risk factors. Although most newly diagnosed patients have no family history of T1DM, un-affected children who have a relative with T1DM are at increased risk as compared to the general population. The most strongly associated susceptibility genes for T1DMare located in the major histocompatibility complex region on chromosome 6 and most likely operate by directing immune development and permitting presentation of autoantigens to autoreactive lymphocytes. A triggering environmental factor probably plays an additional role in evoking clinical disease. This hypothesis is supported by the fact that monozygotic twins are not uniformly concordant for disease progression. Environ-mental factors such as infection may contribute to auto-immune activation by inciting cross-reactivity against antigens on the b-cell that bear a similar molecular structure or in a non-specific way, such as promoting the production of pro inflammatory cytokines that injure islet tissue. The progression from immune activation to clinically relevant islet cell loss may take many years and is marked early by the presence of serum autoantibodies. Once the b-cell mass is insufficient to maintain euglycemia,clinical symptoms evolve. [(4)]

Cure is not available, and patients depend on lifelong insulin injections; novel approaches to insulin treatment, such as insulin pumps, continuous glucose monitoring and hybrid closed-loop systems, are in development. [(5)] Although intensive glycemic control has reduced the incidence of microvascular and macrovascular complications, the majority of patients with T1DM are still developing these

complications. Major research efforts are needed to achieve early diagnosis, prevent β-cell loss and develop better treatment options to improve the quality of life and prognosis of those affected. [6]

Injections of insulin – via subcutaneous injection using either a syringe or using an insulin pump – are necessary for those living with type 1 diabetes because it cannot be treated by diet and exercise alone. Insulin dosage is adjusted taking into account food intake, blood glucose levels and physical activity. Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dL (4.4–7.8 mmol/L). The ultimate goal of normalizing BG is to avoid long-term complications that affect the nervous system (e.g. peripheral neuropathy leading to pain and/or loss of feeling in the extremities), and the cardiovascular system (e.g. heart attacks, vision loss). This level of control over a prolonged period of time can be varied by a target HbA1c level of less than 7.5%. There are four main types of insulin: rapid acting insulin, short-acting insulin, intermediate-acting insulin, and long-acting insulin. The rapid acting insulin is used as a bolus dosage. The action onsets in 15 minutes with peak actions in 30 to 90 minutes. Short acting insulin action onsets within 30 minutes with the peak action around 2 to 4 hours. Intermediate acting insulin action onsets within one to two hours with peak action of four to 10 hours. Long-acting insulin is usually given at the same time once per day. The action onset is roughly 1 to 2 hours with a sustained action of up to 24 hours. Some insulin is biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish. [7]

On the contrary, a physiological, flexible insulin regimen better than a fixed insulin regimen, usually the twice daily split-mixed regimen, protects against the risk of hypoglycemia in relation to food ingestion, physical exercise and sleep. Thus, appropriate education should be delivered at diabetes onset to the child and parents in order to start the strategy of intensified insulin therapy as early as possible. [8]

METHODS

Study design: Data sources was references from reviews in pediatric type 1 diabetes

The inclusion criteria: Studies that included youth under age 19 with type 1 diabetes and a reported association between adherence and glycemic control either with continuous subcutaneous insulin infusion or multiple daily injections were eligible for inclusion.

Exclusion criteria: Articles were not included if they contained youth with type 2 diabetes, had study samples that overlapped with other studies, or the results came from intervention studies.

INSULIN TYPES ACCORDING TO MODE OF ACTION

- **Rapid-acting insulin**

These insulin analogs have a more rapid onset of action (15-30 min) and shorter activity duration (4 to 5 h). Their peak action ranges from 30-90 min post injection. By a single or two amino acid alterations in the insulin molecule, the ability to associate into hexamers is reduced such that they are readily absorbed, however, these modifications do not change the biological properties of these analogs. Examples of rapid acting insulin include Lispro and Aspart. In Insulin Lispro (LysB28, ProB29), the positions of proline at position B28 and lysine at position B29 in the B chain have been reversed.21 In insulin Aspart, the proline at position 28 has been replaced by aspartic acid.22 These rapid acting analogs can be used at mealtime to achieve optimum level of insulin for utilization of glucose released after eating. [9]

- Short-acting insulin

Short acting insulin analogs have an onset of action of around 0.5-1 h, peak action of 2-4 h and activity duration of 6-8 h. Examples of these preparations include Actrapid, Humulin, Hypurin and Neutral. These insulin analogs should be injected into the body 20-30 min before meal so as to get optimum insulin activity for carbohydrate metabolism.

- **Intermediate-acting insulin**

Intermediate acting insulin analogs have an onset of action around 1-2 h, peak action of 6-10 h and activity duration of 10-16 h. Examples of intermediate acting insulin include NPH (Neutral Protamine Hagedorn) and LENTE (from the Latin "lentus," meaning slow, or sluggish) insulin. The absorption rate of NPH insulin is reduced by the addition of protamine to the insulin preparation. In insulin LENTE, the same is achieved by the addition of zinc to the insulin preparation.

- Long-acting insulin

These insulin analogs have an onset of action around 2 h, peak action (sometimes no peak action) of 6-20 h and activity duration of up to 36 h. One way to prolong insulin activity is designing analogs with more positively charged amino acids so as to raise the isoelectric point of insulin to near neutral pH.23 This helps in reducing the solubility of insulin at neutral pH after injection into the body and the absorption into the blood stream will be delayed. Some of the long-acting insulin preparations also have protamine or zinc added to them to increase absorption time. Insulin detemir, also called desB30 insulin, is an example of long-acting insulin. In insulin detemir, the threonine at position B30 in the B chain is removed and a 14-C fatty acid i.e., myristic acid is attached to the lysine at position B29 in the B chain. Attachment of myristic acid helps in insulin hexamer formation and increases the binding of insulin to plasma albumin which delays the free insulin release and which prolongs the activity of insulin. [(10)]

It is important to note that in most cases of DM type 1 diagnosis is made well before the child can manage the disease or foresee future complications. Adolescents are more capable of understanding their disease than young children, but their ability to make responsible decision to a rigid schedule is limited Perhaps the most common medication administered subcutaneously is insulin. While attempts have been made since the 1920s to administer insulin orally, the large size of the molecule has made it difficult to create a formulation with absorption and predictability that comes close to subcutaneous injections of insulin. People with type 1 diabetes almost all require insulin as part of their treatment regimens, and a smaller proportion of people with type 2 diabetes do as well - with tens of millions of prescriptions per year in the United States alone.Insulin historically was injected from a vial using a syringe and needle, but may also be administered subcutaneously using devices such as injector pens or insulin pumps. An insulin pump consists of a catheter which is inserted into the subcutaneous tissue, and then secured in place to allow insulin to be administered multiple times through the same injection site. [(11)]This study is to determine the magnitude of the adherence-glycemic control link in pediatric type 1 diabetes and evaluate its correlates and Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections.

NEW STEPS IN TREATMENT OF TYPE 1 DIABETES MELLITUS

Once the diagnosis of T1DM is established, initial care focuses on restoring euglycemia and teaching the patient and family the basic skills required to take care of diabetes at home. Initial management is influenced by whether the patient is acutely ill at presentation (eg, whether DKA is present). The approach to initial care should also be tailored to the developmental stage of the patient. Ideally, every child newly diagnosed as having T1DM should be evaluated by a diabetes team consisting of a pediatric endocrinologist, nurse educator, dietician, social worker, child life specialist, and mental health professional. At a minimum, during the initial visit with the diabetes team, the family should learn how to check and record blood glucose concentrations using a home blood glucose meter, how to draw up and deliver insulin using a syringe, and how to detect and treat hypoglycemia. Once initial management is completed, care shifts toward on-going management. The patient and family, with the sup-port of the diabetes team, progressively assume greater ownership of diabetes care, with the support of the diabetes team. Ultimately, optimal diabetes management seeks to strike a balance between restoring blood glucose into the euglycemic range in order to minimize the microvascular and macrovascular complications associated with chronic hyperglycemia while simultaneously minimizing a child's unique vulnerability to hypoglycemia. [(12)]

- Initial insulin regimen

Insulin therapy is prescribed to mimic the action of the B-cell by achieving three basic goals:

1. Facilitate metabolism and storage of consumed food. During feeding, insulin is needed to facilitate trans-port of glucose from blood into the cells of insulin-dependent tissues such as muscle, fat, and the liver. In the physiologic state, insulin is secreted almost immediately upon eating. By contrast, insulin therapy inT1DM utilizes subcutaneous delivery of rapid or short-acting insulin with meals and snacks. Usually, the dosage of insulin given is proportional to the amount of carbohydrates being ingested. For example, a patient may take 1 unit of insulin for every 10 grams of carbohydrates being consumed. This insulin-to-carbohydrate (I:C) ratio is titrated frequently during the initial weeks of management, and then routinely during ongoing management. The "Rule of 500"some-times is used to calculate this initial I:C ratio dose bydividing 500 by the estimated total daily dose (TDD)of insulin (estimation of TDD is discussed below).

2. Normalize hyperglycemia. One key to tight glycemic control is to minimize the magnitude and duration of hyperglycemic excursions throughout the day. To accomplish this goal, an additional "correction factor "dose of rapid or short-acting insulin is added to the amount of insulin given to cover carbohydrates at mealtimes. The correction factor dose is

proportional to the degree of hyperglycemia. To calculate the initial correction factor dose, many clinicians will utilize the“Rule of 1,800”by dividing 1,800 by the estimated TDD. The number estimates how much 1 unit of insulin should drop the blood glucose concentration. For example, a patient with estimated total daily dose of18 units of insulin would be expected to have a 100mg/dL drop in blood glucose for each unit of insulin delivered. Therefore, if the target blood glucose level is100 mg/dL, the patient should receive an additional 1unit for a blood glucose of 200 to 299 mg/dL, 2 units for 300 to 399 mg/dL, 3 units for 400 to 499 mg/dL,and so on as a correction factor dose. As with the I: Cratio dose, the correction factor dose is titrated according to the patient’s blood glucose trends.

3. Maintain euglycemia during fasting. Because glucose-increasing counter-regulatory hormones retain their ability to stimulate hepatic glucose production, “basal”insulin is needed to maintain a glycemic balance be-tween meals. For this reason, one or two daily doses of long-acting insulin are given to maintain a low level of insulin during fasting.

When the initial insulin regimen is being designed, it is helpful to approximate the initial TDD of insulin. Children with long-standing diabetes usually require somewhere between 0.5 and 1.0 units/kg per day of insulin. Prepubertal children tend to require a lower TDD, and pubertal children usually need a higher TDD. In most cases, half of the TDD is given as long-acting insulin and the other half is given as rapid or short-acting insulin to cover meals. With the guidance of the diabetes care team, these doses are adjusted empirically for each patient based on the patient’s blood glucose log. It is also important to be mindful of the “honeymoon "phase that follows initial diagnosis and treatment with insulin. During this time, endogenous insulin secretion from remaining b-cells continues, and in many cases, insulin doses must be lowered to prevent hypoglycemia.[13] The honeymoon phase tends to occur more frequently and lasts longer in those patients who are older and have a milder initial presentation. Usually, the insulin dose reaches its nadir at approximately 3 months into therapy and the honeymoon phase ends by 7 months, although this interval is highly variable. This period offers a great opportunity for achieving tight control, and it has been suggested that tight initial control begets improved long-term control. Insulin analogues are categorized by their time course of action as rapid, short, intermediate, or long-acting, as outlined in Table 2 and shown in Figure 1. These pharmacodynamics characteristics form the basis of the frame-work for a daily insulin regimen that seeks to mimic the b-cell. Figure 2 illustrates a “basal–bolus,”or “multiple daily injection "regimens, in which rapid-acting insulin is given with meals and snacks and long-acting insulin to provide a steady amount of insulin with little to no peak between mealtimes. This protocol is the most widely used injection regimen. Short- and intermediate-acting insulin sometimes are utilized in regimens to minimize the number of daily injections. In “mixed-split” regimen, short-acting insulin is mixed in the same syringe with an intermediate analogue, and two daily doses are given—one with breakfast and one with dinner. The short-acting insulin covers breakfast and dinner, while the delayed action of the intermediate-acting insulin is utilized to cover lunch and a bedtime snack. A major ad-vantage of the basal–bolus "regimen over the mixed–split regimen is greater flexibility for when meals and snacks can be eaten and how many carbohydrates can be consumed. Good results can be obtained with a mixed-split regimen, but this treatment requires a patient to eat the same amount at the same time each day. (14).

Table 1: Approximate Pharmacodynamics Characteristics of Insulin Analogues

Insulin analogue	Onset of action	Peak action (h)	Effective duration (h)
Rapid acting			
Lispro (Humalog®, Eli Lilly) Aspart (NovoLog®, Novo-Nordisk) Glulisine (Apidra®, Sanofi-Aventis)	15 min	0.5–1.5	4–6
Short acting			
Regular	30–60 min	2–3	8–10
Intermediate acting			
NPH	2–4 h	4–10	12–18
Long acting			
Glargine (Lantus®, Sanofi-Aventis)	2–4 h	None	20–24
Detemir (Levemir®, Novo-Nordisk)	2–4 h	3–9	6–24*

- Fluid and electrolyte therapy

Once intravenous (IV) access is obtained, water and electrolyte deficits need to be replaced in order to restore the circulating volume and the glomerular filtration rate and improve renal clearance of glucose and ketones from the blood. To replace these deficits, most experts

recommend using isotonic saline initially and caution against re-hydrating the patient too aggressively, suggesting that rehydrating too rapidly using hypotonic solution for initial volume expansion is associated with increased risk for cerebral edema. In general, in children with moderate to severe DKA, initial rehydration with 10 to 20mL/kg isotonic solution (either 0.9% saline or Ringer lactate) over 1 to 2 hours is recommended. Following the initial fluid resuscitation, the rate of IV fluid should be calculated to run at a rate designed to re-hydrate evenly over the next 48 hours. This goal usually can be achieved by running fluids at a rate of 1.5 to 2times the calculated maintenance rate. Because large amounts of replacement with 0.9% saline has been associated with hyperchloremic metabolic acidosis, the IV fluids can be changed to a solution with 0.45% or greater saline with added potassium after at least 4 to 6hours of fluid replacement with iso-tonic solution. As insulin is being replaced, an intracellular shift of potassium that leads to a drop in potassium level is seen. For this reason, frequent monitoring is needed as the potassium is replaced and IV flu-ids are administered.

- Insulin

As the fluid and electrolyte deficitis corrected insulin replacement is needed to normalize the elevated blood glucose and suppress ketogenesis and lipolysis. After the initial 1 to2 hours of fluid rehydration, continuous IV insulin infusion is started ata rate of 0.1 unit/kg per hour. An initial IV insulin bolus is contraindicated and will cause a rapid drop in blood glucose that may precipitate cerebral edema; in addition, IV insulin's half-life is approximately 7 minutes and therefore cannot suppress ketosis. Ideally, the continuous insulin infusion should lead toadropin blood glucose at a rate of 50 to100 mg/dL per hr. In most cases, the hyperglycemia normalizes before the correction of ketoacidosis.

In order to continue infusing insulin to clear the ketoacidosis without inducing hypoglycemia, dextrose can be added to the IV fluids. Many protocols will begin using IV fluids containing 5% dextrose when the blood glucose level drops below 300 mg/dL, then 10% dextrose when blood glucose is less than 200 mg/dL. As insulin continues to be infused and the fluid deficit is re-placed, ketoacidosis will resolve. No other intervention besides insulin and IV fluids is indicated to treat the acidosis; bicarbonate should not be used because its use has been associated with cerebral edema. The continuous insulin infusion should be maintained until the ketoacidosis has resolved (ie, pH greater than 7.30 or bicarbonate-ate greater than 17 mmol/L) and the patient is well enough to tolerate oral intake. At this point, IV insulin can be transitioned to a subcutaneous insulin regimen, as described for the patient who initially presents without DKA. [(15)]

- **Insulin pump**

The insulin pump has increased in popularity as an insulin delivery tool over the past two decades. The essential components of most insulin pumps consist of the pump itself, a disposable insulin reservoir, and a disposable in-fusion set (including a cannula and tubing that connects the cannula to the pump and reservoir). In a manner similar to the basal–bolus regimen, continuous subcutaneous insulin infusion via an insulin pump attempts to mimic the action of the pancreatic b-cell by delivering rapid-acting insulin with basal and bolus components. Most current-generation pumps allow the user to enter in the number of grams of carbohydrates being eaten and the current blood glucose level and then calculate an appropriate bolus dose according to the patient's I:C ratio and correction factor. The pump can also factor in a mathematical estimate of the amount of active insulin in the circulation at the time of the bolus. Instead of using long-acting insulin analogues, the pump delivers basal insulin by slowly infusing frequent, small aliquots of rapid-acting insulin on a continual basis, effectively giving basal insulin as a continuous infusion.

This approach to basal insulin delivery is a key advantage of the insulin pump over multiple daily injections in that it allows different basal rates at various times of day, which can be used to tailor an insulin regimen to fit variations in insulin sensitivity through a daily cycle. For ex-ample, many patients experience an overnight "dawn phenomenon "when circadian rises in growth hormone and cortisol have a glucose-raising effect. To balance this physiologic effect, the overnight insulin basal rate can be titrated up without increasing the daytime basal rate. [(16)]

- **Insulin pens**

The beneficial role of strict glycemic control in people with diabetes has been proven in many large clinical studies and the evidence is getting stronger.1 there has been a tremendous improvement in the number of patients achieving the target glycemic control. This has been made possible as the result of advances in medical science since the discovery of insulin by Banting and Best in 1921. Insulin has been the mainstay of therapy for all subjects with type 1 diabetes and majority of type 2 diabetic subjects. However, there are several barriers to insulin therapy that need to be addressed. One of the most important barriers is the use of conventional insulin delivery process, which remains time-consuming, cumbersome, inconvenient, and to some extent, painful. Furthermore, insulin dosing via syringe is associated with a high risk of dosage errors, with as many as 80% of patients carrying out some aspect of insulin administration via syringe incorrectly.2 Although insulin was discovered almost 9 decades ago, the technology involving the insulin delivery did not see

much of change till the introduction of pen device in 1985. The provisions for insulin delivery have come a long way from very crude and inconvenient metal syringes to the modern pen devices with very fine needles for accurate, flexible, convenient, and virtually painless administration. Insulin pens have the potential to become a major asset for breaking barriers to early initiation of insulin as they overcome many shortcomings of their previous counterparts (Table2).3 Insulin pens have become extremely popular throughout the world; in some countries, 70% to 90% of all insulin is delivered by pen devices.4 Insulin pen devices are unique in that they combine the insulin container and the syringe in a single unit. Some of these pen devices feature an audible click on dose dialing, single-unit dose increments, two-way dose setting, large dials showing the selected dose, and automatic return to zero after dialing the full dose.4 With these state-of-the-art insulin pens, physicians will also find that their efforts are more rewarded, which may hold the key to better long-term outcomes. (17)

- **Stem cell therapy**

Stem Cell Therapy The protocols that guide the differentiation of human-ESCs or iPSCs to pancreatic progenitors in vitro have been perfected during the past decade and entail four stages of differentiation that recapitulate specific developmental stages . Stage 1 is designed to guide the formation of definitive endoderm from PSCs, by mimicking Nodal and Wnt signaling pathways. Activins such as Activin A and Nodal function through binding to Activin I and II receptors which in turn trigger the downstream signaling pathways resulting in activation Smad2/3 proteins. During stage 2 of differentiation, activation of FGF7/KGF or FGF10 signaling is used to induce a posterior foregut phenotype, defined by the expression of HNF1A and HNF1B. The posterior foregut is then specified to PDX1+ cells at stage 3 of differentiation by inhibition of both BMP and SHH pathways and activation of the RA pathway. BMP inhibitors such as dorsomorphin and NOGGIN are used from stage 2 to stage 4 to block hepatic lineage commitment, while SHH inhibitors such as cyclopamine or SANT-1 are added to the culture media to favor pancreatic development. Stage 4 of differentiation leads to the formation of the pancreatic progenitor cells characterized by co-expression of PDX1 and NKX6.1. Generation of hPSC-derived pancreatic progenitors has been achieved using various factors including PKC activators such as EGF, Phorbol 12,13-dibutyrate (PdBu) and ((2S,5S)-(E, E)-8-(5-(4-(trifluoromethyl) phenyl)-2,4-pentadienoylamino) benzolactam (TPB) in combination with Nicotinamide or RA and KGF. The list of signaling pathways targeted to differentiate PSCs towards all pancreatic lineages. hPSC-derived pancreatic progenitors have the potential to generate islet-like structures as well as acinar and ductal cells if transplanted into immunocompromised mice . Remarkably, 16–18 weeks post-transplantation, the hESCderived β-cells generated in vivo are able to restore normoglycemia in diabetic animal models, highlighting the potential of these cells for clinical use. In 2014, two laboratories succeeded in developing monohormonal insulin expressing β-like cells in vitro by adding three additional steps to the differentiation protocol. These two approaches rely on the formation of three-dimensional aggregates grown either in suspension culture or air liquid interface. Briefly, endocrine commitment is achieved at stage 5 by SHH; BMP and ALK5 inhibition coupled with RA and thyroid hormone (T3) stimulation. Stages 6 and 7, which correspond to the formation of insulin-producing β-like cells, require ALK5 and AXL inhibition, as well as the addition of thyroid hormone, T3. Both protocols yield insulin-producing maturing β-like cells, as marked by the expression of PDX1, NKX6.1, NKX2.2, NEUROD1 and MAFA. (18)

INSULIN DELIVERY WITH MDI versus CSII IN ADULTS WITH TYPE 1 DIABETES (19)

- CSII resulted in a significant HbA_{1c}-lowering effect when compared with MDI (mean difference from baseline, -0.30%; 95% CI, -0.58 to -0.02), although results were heavily influenced by one study.
  Strength of Evidence: Low
- Frequency of nocturnal hypoglycemia, severe hypoglycemia, other nonsevere hypoglycemia, hyperglycemia, and weight gain did not differ significantly between CSII and MDI.
  Strength of Evidence: Low
- CSII resulted in a small decrease in postprandial glucose and an increase in symptomatic hypoglycemia when compared with MDI.
  Strength of Evidence: Low
- CSII was associated with a significant improvement in diabetes-specific quality of life when compared with MDI (mean difference, 2.99; 95% CI, 0.006 to 5.97; $p = 0.05$).
  Strength of Evidence: Low

1-Lipohypertrophy and lipodystrophy

Placing the infusion set frequently in the same region can lead to tissue hypertrophy and lipodystrophy. Although these lesions are benign, they can have significant cosmetic effects for patients. Patients should be instructed to frequently rotate the site of infusion set placement to avoid lipodystrophy. Patients should wait 3 to 4 weeks before using the same area to allow appropriate healing time. [(21)]

2-Mechanical Problems

Mechanical problems and interruptions in insulin delivery often cause unexplained highs and can progress to ketoacidosis, if they are not promptly addressed. Possible causes for unexplained highs include infusion-site problems, displaced or clogged infusion set, inactivated insulin because of degradation, or pump malfunction. Troubleshooting should include an investigation of the pump, battery, reservoir, and infusion site to determine the potential causes for unexplained highs or lows. [(22)] Tunneling (insulin return on skin surface) is common when the subcutaneous tissue becomes inflamed and swollen around the infusion site. Blockage of the infusion pipe is also a common problem. Prolonged exposure to heat can cause insulin to coagulate within the infusion set, thereby blocking delivery. Using unbuffered regular insulin increases the risk of infusion-line clogs. Insulin leakage from the tubing or reservoir can also cause unexplainable high blood glucose levels. Although insulin leakage can be difficult to detect, patients can use observation and the distinct smell of insulin to locate the leak. If a clog, leak, or infusion-related issue is suspected, the entire infusion set should be replaced or should be corrected. When the blood glucose rise up to 300 mg/dL or if two consecutive readings are more than 250 mg/dL, the patient should be instructed for ketones test. In addition, a correction bolus dose of insulin should be administered. [(23)] The blood glucose should be monitored every 2 hours, and, if ketones are present, the patient should rehydrate with an appropriate fluid until ketones have cleared and the blood glucose has stabilized. Other reasons for unexplained hyperglycemia or DKA include mechanical problems, illness or infection, incorrect bolus dosing, and degraded insulin. When faced with mechanical problems, the patient may need to remove the insulin pump and correct the error. [(24)]

DISCUSSION

My searches identified 21 studies that met the inclusion criteria show that adherence is linked with glycemic outcomes in pediatric type 1 diabetes, studies including 2492 youth with type 1 diabetes Showed that adherence to an intensive insulin regimen results in improved glycemic control and subsequently, reduced risk of the long-term complications of the disease A number of study and sample characteristics were examined as factors associated with this relationship between adherence and glycemic control. There were no sociodemographic (age, ethnicity) or disease (duration and A1c levels) characteristics.

Study conducted at the Yale Children's Diabetes Clinic, of patients who met the following criteria: ages 12 to 20 years, with no other health problem, patients were divided into two groups' first group on continuous subcutaneous insulin infusion (CSII) and second group on multiple daily injections (MDI). In both groups, the largest decrease in HbA1c occurred within the first 6 months. During 6 to 12 months, HbA1c levels rebounded modestly in the MDI but not in the CSII group ($p<0.05$) by the end of 12 months, patients using CSII used significantly less insulin than the MDI group ($p=0.009$). [(19)]

CSII patients had 50% fewer severe hypoglycemic events than MDI patients ($p<0.01$). Patients in both groups experienced weight gain, with no significant difference between groups.Psychosocial outcomes at 12 months, patients using CSII found it easier to cope with diabetes than those using MDIs ($p=0.05$).Although both groups of adolescents achieved better glycemic control, the CSII group was able to maintain this control much better than the MDI group. [(20)]

CONCLUSION

Medium-sized association across studies including 2492 youth with type 1 diabetes was 0.28; as adherence increases, A1c values decrease. Considering that the DCCT clearly showed that adherence to an intensive insulin regimen results in improved glycemic control and subsequently, reduced risk of the long-term complications of the disease

These findings suggest that all children and adolescents with type 1 diabetes should experience better glycemic outcomes with adherence promotion; insulin pumps provided better glycemic control, fewer adverse events, and better psychosocial outcomes than MDIs

Majority of the patients and families chose to continue with CSII after the completion of the studies, even in studies where insulin pumps showed no objective benefit .

References

1. "Causes of Diabetes". National Institute of Diabetes and Digestive and Kidney Diseases. June 2014. Archived from the original on 2 February 2016. Retrieved 10 February 2016.
2. Chiang JL, Kirkman MS, Laffel LM, Peters AL (July 2014). "Type 1 diabetes through the life span: a position statement of the American Diabetes Association". Diabetes Care. 37 (7): 2034–54. doi:10.2337/dc14-1140. PMC 5865481. PMID 24935775.
3. Bluestone JA, Herold K, Eisenbarth G (April 2010). "Genetics, pathogenesis and clinical interventions in type 1 diabetes". Nature. 464 (7293): 1293–300. Bibcode:2010Natur.464.1293B. doi:10.1038/nature08933. PMC 4959889. PMID 20432533.
4. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. The Lancet. 2014 Jan 4;383(9911):69-82.
5. Ilonen J, Hammais A, Laine AP, Lempainen J, Vaarala O, Veijola R, Simell O, Knip M. Patterns of β-cell autoantibody appearance and genetic associations during the first years of life. Diabetes. 2013 Oct 1;62(10):3636-40.
6. "Chronic diseases and their common risk factors" (PDF). World Health Organization.. Archived (PDF) from the original on 2016-10-17. Retrieved 30 August 2016
7. Shrivastava SR, Shrivastava PS, Ramasamy J (March 2013). "Role of self-care in management of diabetes mellitus". Journal of Diabetes and Metabolic Disorders. 12 (1): 14. doi:10.1186/2251-6581-12-14. PMC 3599009. PMID 23497559.
8. Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2diabetes mellitus: clinical and biochemical differences. Arch InternMed. 2014;164(17):1925–1931
9. Ahmad K. Insulin sources and types: a review of insulin in terms of its mode on diabetes mellitus. Journal of Traditional Chinese Medicine. 2014 Apr 15;34(2):234-7.
10. Gedawy A, Martinez J, Al-Salami H, Dass CR (February 2018). "Oral insulin delivery: existing barriers and current counter-strategies". Journal of Pharmacy and Pharmacology. 70 (2): 197–213. doi:10.1111/jphp.12852. PMID 29193053. S2CID 12848146.
11. Taylor C (2011). Fundamentals of nursing : the art and science of nursing care (7th ed.). Philadelphia: Wolters Kluwer Health and Lippincott Williams & Wilkins. ISBN 978-0781793834.
12. McCrimmon RJ, Sherwin RS. Hypoglycemia in type 1 di-abetes. Diabetes. 2010;59(10):2333–2339
13. American Diabetes Association. Standards of medical care indiabetes—2011. Diabetes Care. 2011;34(Suppl 1):S11–S61
14. Diabetes Fact sheet N°312". WHO. October 2013. Archived from the original on 26 August 2013. Retrieved 25 March 2014.
15. Krishnasamy S, Abell TL (July 2018). "Diabetic Gastroparesis: Principles and Current Trends in Management". Diabetes Therapy. 9 (Suppl 1): 1–42. doi:10.1007/s13300-018-0454-9. PMC 6028327. PMID 29934758.
16. Asakura T, Seino H, Kageyama M, Yohkoh N. Evaluation of injection force of three insulin delivery pens. Expert Opin Pharmacother 2010;10:1389-93.
17. Nostro MC, Sarangi F, Yang C, Holland A, Elefanty AG, Stanley EG, et al. Efficient generation of NKX6-1+ pancreatic progenitors from multiple human pluripotent stem cell lines. Stem Cell Reports. 2015;4(4):591–604.
18. Overstreet S, Holmes CS, Dunlap WP, Frentz J. Sociodemographic risk factors to disease control in children with diabetes. Diabet Med. 1997;14(2):153–157
19. . La Greca AM, Follansbee DM, Skyler JS. Developmental and behavioral aspects of diabetes management in youngsters. Child Health Care. 1990;19(3):132–139
20. Chisholm V, Atkinson L, Donaldson C, Noyes K, Payne A, Kelnar C. Predictors of treatment adherence in young children with type 1 diabetes. J Adv Nurs. 2007;57(5):
21. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. Diabetes care. 1999 Nov 1;22(11):1779-84.
22. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, Wei J, Narayan KM, Ali MK (December 2017). "Long-term Sustainability of Diabetes Prevention Approaches: A Systematic Review and Meta-analysis of Randomized Clinical Trials". JAMA Internal Medicine. 177 (12): 1808–17. doi:10.1001/jamainternmed.2017.6040. PMC 5820728. PMID 29114778.
23. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA (April 2018). "Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians". Annals of Internal Medicine. 168 (8): 569–576. doi:10.7326/M17-0939. PMID 29507945.
24. Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symp-tomatic hypoglycaemia in 411 type 1 diabetic patients. Diabet Med.2011;8(3):217–22