

# **The Management of Insulin-dependent Diabetes Mellitus**

**Andrew Ealovega  
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Diabetes Mellitus is a metabolic disorder associated with great morbidity and mortality. According to the American Diabetes Association, about 16 million Americans have diabetes, with up to 675,000 being insulin-dependent (also known as Type 1 or Juvenile-Onset Diabetes) [1]. Short-term complications of diabetes include coma and possible death from hypoglycemia (low blood sugar), and ketoacidosis, which can lead to coma and death from hyperglycemia (high blood sugar). Long-term complications are a result of microvascular and macrovascular manifestations. These changes can cause devastating complications to the eyes (retinopathy), nerves (neuropathy), kidneys (nephropathy), and to the large blood vessels that supply the body, especially the head and heart.

The optometrist's role in providing eye care to diabetics is essential, but their knowledge needs to go beyond the proper diagnosis and treatment of ocular complications. Diabetes is not a disease that is simply treated. It is a lifelong process that must be managed every day. Optometrists need to be knowledgeable about the management of diabetes so they can better understand, communicate with, and educate their patients. Optometrists also need to be able to communicate with other doctors and become part of their patient's management team. The Diabetes Complication and Control Trial (DCCT) showed that keeping blood glucose close to normal can prevent complications in patients without any, and discontinue or even reverse the process in those patients with complications. The DCCT concluded that a team including endocrinologists, nurses, dietitians, social workers and other specialists needs to work together to manage diabetes [2,3]. If optometrists are to be part of this team, then they must understand the

management of diabetes. The primary treatment of retinopathy, and other long-term complications, needs to be prevention first, then proper treatment later if they occur. This paper will discuss specifically the management of insulin-dependent diabetes mellitus.

Insulin-dependent Diabetes Mellitus (IDDM) is a condition that is characterized by a reduced or total lack of insulin production. This type of diabetes is also referred to as Type 1 or Juvenile-Onset Diabetes. IDDM usually affects people less than thirty years old, with a peak onset from eleven to thirteen years old. Insulin is produced and stored by the Beta cells in the Islets of Langerhans of the pancreas. In insulin-dependent diabetes these Beta cells are destroyed, and therefore, insulin injections are always required to replace the body's naturally produced insulin. The etiology of diabetes is not completely understood, but it is thought to be an autoimmune process. Anti-islet and anti-insulin antibodies can be found in individuals with IDDM before they have any other signs or symptoms of the disease. Current research is looking at ways of preventing diabetes in people who have these antibodies [4].

Insulin is a hormone that allows cells to take in and use energy stored in blood glucose. This glucose can start as simple sugars or complex carbohydrates. Without the insulin, the glucose builds up in the blood causing hyperglycemia. The lack of insulin leaves the cells without the energy they need. The body then oxidizes free fatty-acids to get energy and as a result releases ketone bodies into the blood. The ketone bodies along with B-hydroxybutyrate and acetoacetate, cause the blood to become acidic. This is called ketoacidosis. Ketoacidosis is a serious acute condition that can cause coma and lead to death. At the same time, the kidneys cannot filter out the excess sugar in the blood and it

“spills” out into the urine, taking extra water with it. These processes lead to the classic symptoms of polyuria (excessive urination), polydipsia (excessive thirst), and polyphagia (excessive hunger), along with weight loss. Daily insulin injections are needed to correct this situation.

After the acute danger is over, the diabetic must establish glycemic control to prevent the long-term microvascular and macrovascular complications associated with insulin-dependent diabetes [2,3,5]. This is accomplished by a combination of multiple daily insulin injections (or a subcutaneous infusion pump), home blood glucose monitoring, diet, exercise, education, and close work with a team of specialists.

There is currently no cure for IDDM. This is a condition that must be managed. Although there are many important aspects to managing diabetes, insulin injection is the one treatment aspect that is necessary for the others to work. A normally functioning pancreas secretes a constant low level of insulin called a basal level. After a meal the body will secrete an additional proper amount of insulin for that meal. If the blood glucose level gets too low, the pancreas secretes the hormone glucagon that signals the liver to release stored glucose into the blood. In this way the body regulates and maintains the blood glucose level at the appropriate amount.

The diabetic must use insulin injections to replace the pancreas' function. There are different types of insulin to help maintain glucose levels. These are short-acting, intermediate-acting, long-acting, and a newly developed rapid-acting insulin. Regular insulin is a short-acting insulin. It starts working 30 to 60 minutes after injection and peaks after 2 to 3 hours. Regular insulin continues to work for up to 8 hours after



injection, with some residual effect reported up to 16 hours later [6]. Because regular insulin takes at least 30 minutes to start working, it needs to be injected at least 30 minutes before eating or hyperglycemia will result after the meal.

NPH and Lente are intermediate-acting insulins. These are regular insulin with an added component to delay the absorption and increase the length of action. NPH stands for Neutral Protamine Hagedorn. Protamine is a protein used to delay the absorption and Hagedorn is the name of its developer. Lente has added zinc to slow its absorption. These intermediate-acting insulins take 1 to 3 hours to start working, peak in 6 to 12 hours, and may continue for up to 24 hours [7].

Ultralente is a long-acting insulin. It also has added zinc to prolong its effects. Ultralente does not start working for 4 to 8 hours; it has a long low level peak from 12 to 18 hours and continues to work for up to 28 hours after injection [7].

Most insulin treatment regimens call for a mixture of short-acting and intermediate-acting insulins. The patient can mix these in the syringe or buy them in a premixed fixed-ratio combination. These are mixtures of regular and NPH and come in 70/30 (70% NPH with 30% R) or 50/50 (50% NPH with 50% R) ratios.

Insulin also comes in different concentrations. Insulin is measured in units. The amount of units per cubic centimeter determines the concentration. Most insulin in the U.S. is U-100 (100 units per cubic centimeter), although other concentrations are available. The proper syringe must be used with each concentration of insulin for proper measurement. Insulin also comes from various sources. Insulin originally came from

animal sources, mainly beef or pork. Today most insulin has a human source. This is produced by a recombinant DNA process.

Fluctuations in the rate of insulin absorption lead to unpredictable glucose levels. Absorption rates can vary for several reasons. When the insulin is longer acting, the absorption rate becomes more variable. Absorption rates in an individual can vary up to 25% from one day to the next. Absorption rates also change with different injection sites and with exercise of the muscles at the injection sites. The fluctuation in absorption time leads to frustration and unexplained glycemic levels [7].

Recently a new rapid-acting insulin was introduced. This new insulin is Lys(B28), Pro(B29) human insulin, which is commonly called Lispro. This is being produced and marketed by Eli Lilly and Co. under the name Humalog [6]. Lispro is currently available by prescription only, as compared to the other insulins that are available over the counter. This rapid absorption and peak in action are achieved by reversing the amino acids at the 28 and 29 positions of the insulin B chain. These are the amino acids proline and lysine. The result is an insulin with a rapid onset of 10 to 15 minutes and a peak effect at about 50 minutes. This is much quicker than regular insulin that takes 30 to 60 minutes to start working and does not peak for 2 to 4 hours. Lispro also has a shorter and more consistent length of action of 4 hours, as compared to regular insulin that can have residual effects reported up to 16 hours later.

In studies comparing the effectiveness of Lispro to regular insulin, Lispro significantly reduced the rise in the blood glucose level at the point 2 hours after a meal [8]. Subjects in the studies also reported significantly less hypoglycemic episodes when

using Lispro as compared to regular insulin [9]. This may be due to the fact the Lispro has a shorter duration of action. Lispro finishes working in 4 hours, but regular insulin can have a much longer residual effect. If a patient is on multiple injections of regular insulin each day, this residual effect can build up and cause hypoglycemia, even though it is a short-acting insulin. One of the adverse effects of intensive therapy in the DCCT was an incidence of hypoglycemia that was three times greater than normal. The use of Lispro, instead of regular insulin, during intensive therapy could help eliminate this negative side-effect.

Even though there was not a clinically significant difference in hemoglobin A1c (average blood glucose) levels between patients using Lispro and those using regular insulin in clinical studies, Lispro may help achieve normal glycemic control outside the clinical setting [6]. During clinical trials, the patients taking regular insulin stuck to a strict regimen of pre-meal injections at 20 to 40 minutes before eating. In real life it is often difficult to plan when meal times will be, especially when at work, going out to eat, or when getting ready for work in the morning. Diabetics often give injections immediately before eating or even after a meal. This results in post-meal hyperglycemia, which can lead to an increase in HbA1c levels and an increased chance of long-term complications. Rapid-acting Lispro would help eliminate this problem because it begins working within 10 to 15 minutes. However, because Lispro has a short duration of action, it is necessary to combine its use with an intermediate or long-acting insulin to maintain a basal level of action. With these beneficial therapeutic actions, Lispro can help achieve the goal of the DCCT of normal glycemic control [6,8,9].



The primary method of measuring long-term glycemic control is the glycosylated hemoglobin test [10]. The specific test used in the DCCT was the hemoglobin A1c. Both of these tests measure the same thing, but have a different scale to report the results. The HbA1c (hemoglobin A1c) measures the average blood glucose level over approximately the last four months. Glucose binds itself to hemoglobin in the blood. To determine the average blood glucose level, one measures the percentage of this glycosylated hemoglobin. This provides a much better evaluation of long-term glycemic control than random or fasting glucose levels, which only give a glucose level for one moment. Because the HbA1c is an average, someone could have widely fluctuating blood glucose and have a good HbA1c result [11]. The patient and management team should assess glycemic control with both HbA1c results and home blood glucose monitoring. This gives both an average glucose level and daily fluctuations in glucose level. Normal HbA1c levels are from 4% to 6%. Figure (1) compares average blood glucose to glycosylated hemoglobin and hemoglobin A1c. Glycosylated hemoglobin testing is the standard of care for evaluating glycemic control in diabetics.

Average Blood Sugar (mg/dl)	% Glycosylated Hemoglobin	% Hemoglobin A1c
60		4%
90	8%	5%
120	9%	6%
150	10%	7%
180	11%	8%
210	12%	9%
240		10%
270	13%	11%
300	15%	12%
330		13%

**Figure 1. Comparison of average blood sugar to % glycosylated hemoglobin and % hemoglobin A1c.** *From American Diabetes Association [1].*



Although no study has proven that exercise alone improves glycemic control in IDDM patients, exercise has long been considered an integral part of IDDM management. Exercise is important for many reasons. One of the most important benefits is that it lowers many of the risk factors for cardiovascular disease, which causes the majority of deaths in diabetics [12]. Other benefits of exercise are an increase in insulin sensitivity and an increase in metabolic rate, which together can lower blood glucose levels [12]. This is a complex process that requires adjusting insulin intake and diet according to exercise intensity in order to maintain a normal glucose level. If too much insulin is present, or even the proper amount for non-active behavior, then exercise will result in hypoglycemia. On the other hand, if not enough insulin is present, then exercise may make hyperglycemia worse.

When a non-diabetic exercises, the body reduces insulin secretion. Patients with IDDM must decrease their insulin by 30-50% depending on the type and length of time of activity [13]. The liver usually releases glucose during exercise to maintain normal sugar levels. Non-esterified fatty acids are also released from adipose tissue for energy. If the patient does not reduce insulin levels, then both of these processes are inhibited. This, along with an increase in glucose uptake by active muscles, leads to hypoglycemia.

When planning exercise, frequent blood glucose monitoring is necessary. Depending on the glucose level before exercise, the diabetic may require additional carbohydrates to avoid hypoglycemia [12,13]. Although guidelines are available suggesting the amount of additional carbohydrate and insulin reduction required for different activities, these are extremely variable from one person to the next. Through trial and error, each individual must come up with a plan that complements his or her exercise program.

Insulin absorption increases when injected over a working muscle. Diabetics inject insulin in the thighs, buttocks, abdomen, or arms. The quickest and most consistent absorption is from the abdomen. The abdomen is also the site at which insulin absorption is the least affected by exercise. Therefore, injections before exercise should avoid the areas being exercised to decrease the chance of hypoglycemia [7].

Exercise continues to lower blood glucose levels for several hours after exercise. During exercise, muscles deplete their glycogen stores. After exercise, the muscles must replace this stored glucose. This is beneficial because it can help lower blood glucose levels, but if excessive, can lead to hypoglycemia.

Unfortunately, exercise is not always planned. This is especially true with children. In these unanticipated times of exercise, hypoglycemia is a risk. A person with IDDM should always carry some form of simple sugar on them to counter-act hypoglycemia.

Exercise can cause an increase in hyperglycemia and ketosis in insulin-dependent diabetics who are in poor control and have decreased insulin levels. Insulin-dependent diabetics in poor control have an increase in fatty acid oxidation that leads to increases in ketone bodies in the blood. The body's normal reaction to decreased insulin levels while exercising is to release glucose into the blood and increase the breakdown of fatty acids. Thus a diabetic with low insulin levels who is already in poor control will end up with a worsening of hyperglycemia and ketosis. Therefore, diabetics should not attempt exercise when they are in poor control or have ketone bodies present [12,13].

Diet is an integral part of IDDM management, but it is often also the most frustrating [14,15]. Ideally, patients plan meals to coordinate with the appropriate time and amount of

insulin. This is easier said than done. In 1950, a food exchange system was developed to aid in comparing the energy content of food. In this program the amount of food equaling one exchange is given for each particular food within the food group. Any two exchanges within a food group should contain the same nutritional content. For example, one fruit exchange may be 1/2 cup of orange juice, 1/4 cup of grape juice, or a small apple. Each of these examples contains 15 grams of carbohydrates. Patients, using exchange lists for each of the food groups, develop a diet that allows them a certain amount of exchanges of each food group at each meal. Together, the doctor, dietitian, and patient determine the total energy content of each individual's diet. This diet is very strict and often confusing to the patient. The result is usually non-compliance by the patient, who either totally ignores the diet or develops his or her own modified version of the diet [14,15].

Another form of diet is simply to count the total carbohydrates in a meal and base the insulin dose on this amount [15]. Because carbohydrates are the main cause of blood glucose fluctuation, the emphasis is on total carbohydrate count regardless of the source of the carbohydrates. It is still important with this system to keep total carbohydrate content at a particular meal and mealtime consistent.

Recent studies have shown that patients on intensive therapy may practice a more liberalized diet without a worsening of glycemic control. Liberalization of a patient's diet is not a problem as long as the patient adjusts insulin levels to match food intake [16].

Diabetics should use certain foods in moderation to avoid an increase in complications [14]. Sodium can cause an increase in blood pressure, which can make both retinopathy and nephropathy worse. Patients with nephropathy should limit protein intake to avoid additional



kidney damage. A low fat diet is beneficial in preventing complications associated with macrovascular disease.

The completion of the Diabetes Control and Complication Trial (DCCT) in 1993 proved that keeping blood glucose at a near normal level could prevent and slow the progress of the long-term complications of retinopathy, neuropathy, and nephropathy in patients with insulin-dependent diabetes [2,3,5]. In the past many people associated high blood glucose with long-term complications, but no one was sure if controlling glucose levels would prevent the complications or if they were secondary to some other mechanism. One thousand four hundred forty-one volunteer patients with IDDM were randomly assigned to either a conventional therapy group or an intensive therapy group (this is also referred to as intensive insulin therapy, but because it involves much more than just insulin, it is referred to as intensive therapy). The goals of these two groups were very different. The goal of the conventional therapy group was the absence of symptoms associated with hyperglycemia and hypoglycemia, the absence of ketonuria, and normal growth and development. The goal of the intensive therapy group was to have blood glucose levels as close to normal as possible. This included pre-meal glucose readings of 70 to 120 mg per deciliter, post-meal readings less than 180 mg per deciliter, weekly 3:00 a.m. readings above 65 mg per deciliter, and a monthly HbA1c less than 6.05 (within the normal range) [2,3].

Conventional therapy consisted of education about diet and exercise, up to two daily injections of mixed short and intermediate-acting insulins, and daily blood or urine testing. The injections usually remained fixed amounts and did not change to accommodate different glucose levels. Some examples of fixed-dose conventional insulin injection patterns would include the following: (1) a single morning injection of intermediate or long-acting insulin, (2) a single

morning injection of short-acting insulin mixed with an intermediate-acting insulin, or (3) a morning injection of short and intermediate-acting insulins and a before-dinner injection of short and intermediate-acting insulins [7]. Each step in this progression provides a little more control by supplying an extra peak of insulin at appropriate times. The first and second examples, with only a single injection, do not mimic the body's normal insulin secretion and provide poor glycemic control. The third example provides better insulin availability, but requires rigid meal times and consistency in eating habits. If the patient misses or delays lunch, then the intermediate-acting insulin will cause hypoglycemia to occur. Another disadvantage to this regimen is that the intermediate insulin has a gradual peak in action and may not be enough coverage for lunch.

Intensive therapy accomplished its goals through close work with a team of doctors, nurses, dietitians, and social workers to develop personalized exercise, diet, and injection strategies [2,3,5]. Patients could use multiple daily injections of any pattern or a subcutaneous insulin infusion pump to deliver the insulin. One major difference is that the amount of insulin is not a fixed amount. With the use of home blood glucose monitoring of at least four times a day, the patient adjusts the amount of insulin given to an appropriate amount depending on the glucose level at the time of injection. The team develops a personalized scale so that the patient knows how much insulin to give for each glucose level. This is either called a sliding scale or algorithm. It is important for patients to measure their blood glucose before each meal and before bedtime and to stay in close contact with their doctors. Not only is it important for patients on intensive therapy to test their blood glucose so they know how much insulin to give, but by keeping a record, they can look for patterns of hyperglycemia or hypoglycemia [7]. If they find a pattern,



then the patients can adjust the sliding scale up or down to correct the problem. Another aspect of intensive therapy is adjusting the insulin amount to reflect planned activity or changes in food intake. This makes intensive therapy more flexible than conventional therapy and tries to match the insulin intake to the current needs. Intensive therapy attempts to mimic the body's natural response to fluctuations in blood glucose level.

Intensive therapy with multiple daily injections has two main patterns [7]. The first is regular insulin given before each meal and an intermediate-acting insulin given at night. The regular insulin often has a long enough action time to act both as a short-acting insulin to cover the meal and as a supply of a basal amount until the next meal and injection. The intermediate insulin supplies coverage during nighttime and can be given either with the dinner injection or before going to bed. The second choice is to give regular insulin before each meal and long-acting Ultralente both in the morning and at dinnertime. The regular insulin provides coverage for the meals and the Ultralente provides an almost peakless, constant, basal level. This second pattern helps people who are having hyperglycemic fluctuations, but does not have as much coverage for the morning hours as the first pattern using an intermediate-acting insulin at bedtime. The key to intensive therapy is to tailor each patient's diabetes management to meet his or her particular needs and goals. Although this requires more involvement by both the patient and the doctor, it leads to more flexibility in lifestyle.

Intensive therapy patients in the DCCT could also choose to use an insulin pump. This is also referred to as CSII (continuous subcutaneous insulin infusion). A CSII regimen closely mimics the body's normal insulin secretion [7]. Because CSII only uses regular insulin there is less day to day fluctuation in absorption rate. A constant, small amount of insulin released by the



pump provides a basal level of insulin. At meal times the user initiates the pump to release a bolus of insulin. Through self-monitoring of blood glucose level, anticipating meal size, and planning exercise, patients determine the amount of insulin needed. This is similar to the multiple daily injection regimens. Tubing delivers the insulin to a small needle placed under the skin, usually in the abdomen. The needle and infusion set need to be cleaned and changed every 24 to 72 hours. Patients can also program these pumps with different basal rates for different times of the day and specific activities.

The intensive and conventional therapy groups in the DCCT contained two subgroups [2,3]. The first subgroup was the primary prevention group. The purpose of this group was to study if keeping blood glucose levels normal could prevent complications associated with IDDM in patients who had no complications at the start of the study. The second subgroup was the secondary intervention group, designed to study if normalization of glycemic control could slow or stop the progression of complications already present at the beginning of the study.

After nine years, researchers completed the study a year early because the results were so promising. Intensive therapy reduced the risk of retinopathy, neuropathy, and nephropathy in both the primary and secondary intervention groups. The average blood glucose level for all readings in the intensive therapy group was 155 +/- 30 mg per deciliter, with an average HbA1c percentage of about 7.2%. The average blood glucose level for all readings in the conventional group was 231 +/- 55 mg per deciliter, with an average HbA1c percentage of about 9.6% [2,3,5].

Intensive therapy reduced the prevalence of retinopathy in the primary prevention group by 76%. In the secondary intervention group of intensive therapy, retinopathy was reduced by an average of 54%. Intensive therapy reduced clinical neuropathy at five years by 69% in the

primary prevention group. In the secondary intervention group, intensive therapy reduced clinical neuropathy at five years by 57% [2,3,5].

When studying nephropathy, researchers considered the incidence of both microalbuminuria (urinary albumin excretion  $\geq$  40 mg per 24 hours) and albuminuria (urinary albumin excretion  $\geq$  300 mg per 24 hours). Intensive therapy reduced the risk of microalbuminuria by 34% and albuminuria by 44% in the primary prevention group. Intensive therapy reduced the risk of microalbuminuria by 43% and albuminuria by 56% in the secondary intervention group [2,3,5].

Because of the young age of the patients and the low incidence of macrovascular disease, there were no clear results on the prevention of macrovascular disease with intensive therapy.

The primary adverse effect of intensive therapy is hypoglycemia [2,3,5]. During the DCCT, the intensive therapy group had three times greater risk of hypoglycemia than the conventional therapy group. Hypoglycemia poses the greatest risk at night during sleep. If a patient fails to wake up, then severe hypoglycemia can result. According to the American Diabetes Association, the risk of hypoglycemia makes intensive therapy contraindicated in children less than two years old, and implemented with caution between the age of two and seven years [5]. At this age, hypoglycemia may impair normal brain development. Intensive therapy in children is more difficult, and the risk of hypoglycemia greater, because adherence to diet, activity levels, and treatment plan is often not reliable.

Another adverse effect of intensive therapy is weight gain [2,3,5]. The exact reason for the weight gain is not known. Two possible causes are that patients ate more because of greater

flexibility in their diets on intensive therapy and that patients ate more to treat hypoglycemic attacks.

In some patients, intensive therapy worsened existing retinopathy [2,7]. In most cases the increase in retinopathy was temporary and the effects went away after 18 months of intensive therapy. The risk of increased retinopathy should not stop a patient from starting intensive therapy, especially considering that the secondary intervention group of intensive therapy had a 54% reduction in retinopathy.

Intensive therapy may not be for everyone. It requires a great amount of education, motivation, and self-care. Even if a patient with IDDM does not want to participate in an intensive therapy program similar to the one in the DCCT, any improvement that a patient makes in their glycemic control will lower the risk of long-term complications.

Insulin-dependent diabetes for the most part is a self-managed condition, with guidance supplied by a management team. Without proper motivation, education, or financial ability to participate in his or her diabetes management, the patient will have poor glycemic control [17]. Even though the DCCT demonstrated that intensive therapy will reduce the risks of complications, most patients do not participate in intensive therapy. Many patients and doctors do not have the resources supplied during the DCCT available to them [17]. The family doctors who work with many diabetic patients often do not have the time or knowledge to implement intensive therapy.

Intensive therapy has increased costs associated with more frequent doctor visits and extra supplies required to monitor and manage IDDM. In the long term, intensive therapy provides reduced costs by decreasing complications associated with decreased work productivity,



specialized surgery and continued advanced care. In an era of managed care systems struggling to slow the rise in the cost of health care, one can only hope that the long-term benefits will be recognized and will outweigh the short-term cost of intensive therapy [18].

One of the most important aspects of IDDM management is patient participation and decision-making in every aspect of his or her care [19]. This includes optometric care. Hopefully, optometrists will continue to broaden their knowledge of IDDM so they can better comprehend the complexities of its management and participate in the care of their insulin-dependent diabetic patients.

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