Management of Diabetes in the Real World: Tight Control of Glucose Metabolism

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This clinical review looks at tight control of blood glucose with oral agents and insulin in adults and children with type 2 diabetes mellitus. It includes recommendations based on the treatment algorithms from the Texas Diabetes Council. The focus is on specific indications for selecting initial monotherapy, early dual therapy, or combination oral therapy. Discussion includes glycemic targets and times to goal along with recommendations for insulin management that depend on patient stratification as “treatment naïve” or “combination oral agent failures” (defined as A1c value ≤9.5% or >9.5%). This presentation also includes protocols for once-daily injections, multidose insulin injections, and intensive insulin therapy (physiologic insulin delivery) as well as discussion of starting doses, titration schedules, optimum basal bolus insulin regimen, and calculation of insulin augmentation.

Diabetes mellitus has reached epidemic proportions worldwide. In the United States, approximately 30% of Americans older than 60 years have type 2 diabetes mellitus (T2DM) or impaired fasting glucose (IFG). The prevalence of T2DM now shows a 30% increase in people aged 50 to 59 years, a 40% increase among those between the ages of 40 to 49 years, and a 70% increase in those 20 to 39 years old.1,2 During the past decade, the incidence of T2DM is thought to have increased more than 300% in children between the ages of 8 and 19 years.3 Note that the greatest rates of increase are in the young. The cardiovascular and microvascular complications of diabetes are well known to all physicians. Are we ready to treat teenagers with anterior wall myocardial infarctions?

How and when should we intervene when a person is at risk for diabetes? Major studies to date indicate that diabetes can be prevented with education, nutrition, and exercise. Results from the Diabetes Prevention Program,4 the Diabetes Prevention Study,5 Da Qing,6 and the Diabetes Epidemiology: Collaborative Analysis Of Diagnostic criteria in Europe (DECODE)7 all showed that prevention works. In fact, diet and exercise interventions are changing rapidly. It appears likely that recommendations may be forthcoming to consider using metformin, orlistat, or acarbose for people with impaired glucose tolerance or IFG.8 Clinical trials are in progress evaluating whether sulfonylureas, metformin, the thiazolidinediones, or combination oral modes of therapy would be beneficial. It is not known if early interventions with oral medications will reverse early changes in glucose metabolism or prevent their progression to T2DM. Hence, the oral agents are not approved by the Food and Drug Administration (FDA) for patients with plasma glucose levels of less than 126 mg/dL.

If T2DM is diagnosed, early and aggressive intervention is indicated. New recommendations for initiation of therapy for patients with T2DM are shown in Figure 1. The algorithm in Figure 1 is from the Texas Diabetes Council.12 It has been reviewed widely in the United States and has achieved much acceptance throughout the country. This algorithm is used if a person has an FPG level that is less than 260 mg/dL and is asymptomatic. Targets for therapeutic interventions are shown in the upper left box. Ranges are indicated for A1c,
FPG, fasting self-monitored blood glucose, and 2-hour postprandial glucose levels to remain consistent with the American Diabetes Association (ADA)9 and the American College of Endocrinology13 guidelines.

Note the time frames in which to achieve glycemic goals (Figure 1). Only 1 month is recommended to achieve glycemic targets using the cornerstones of therapy: education and nutrition and exercise. If goals are not met in 4 weeks, therapeutic intervention is indicated. Initial therapy can be with a sulfonylurea, metformin, a thiazolinedione (TZD), a meglitinide, or an α-glucosidase inhibitor if the FPG level is less than 210 mg/dL or the A1c concentration is less than 9.0%. Metformin should be selected if the patient is overweight or dyslipidemic.

**Initiating Treatment With Combination Therapy**

Many clinicians use combination therapy as the initial therapy, especially in the asymptomatic patient with glucose levels of greater than 210 mg/dL or an A1c value that is greater than 9.0%. If the patient is on monotherapy, glycemic targets should be reached within 3 months; if not, combination therapy is indicated. If the patient starts on combination therapy, glycemic targets should be reached within 3 to 6 months. If the patient is not at goal by 6 months, insulin is recommended.

It is important to realize that oral therapy should be started in patients with diabetes if the FPG level is 110 mg/dL to 130 mg/dL, or the patient’s glucose records indicate that the fasting glucose level is 100 mg/dL to 120 mg/dL. Therapeutic interventions should be advanced within one or two A1c cycles to achieve glycemic goals. The same recommendations hold for T2DM in children. Note that metformin is the only oral diabetic agent approved by the FDA for children aged 10 years and older; however, other oral agents may be used at the discretion of the clinician.

**Insulin Therapy**

Insulin therapy is indicated in patients who have not achieved control (A1c <6.5% to 7.0%; FPG <110 mg/dL to 130 mg/dL) using combination oral hypoglycemic agents after 3 to 6 months.

When initiating insulin therapy, do not stop any of the oral agents. If the patient is taking an insulin sensitizer(s), it should be continued. In fact, sensitizers are indicated in patients with T2DM using 2 units of insulin per kilogram of body weight, or more than 100 units of insulin per day. The role of insulin secretagogues (sulfonylureas and meglitinides) is less clear. Common experience suggests that the sulfonylurea or repaglinide/nateglinide should be continued at least 3 to 6 months. When glycemic control is established, decisions can be made about weaning the patient off the secretagogue. Over time, it is difficult to argue that a person requires insulin injections and drugs to induce release of endogenous insulin.

Insulin therapy is indicated for treatment naïve patients if their initial glucose level is greater than 260 mg/dL and they are asymptomatic. Both a basal and a short-acting insulin are indicated for patients with type 1 diabetes mellitus (T1DM). Oral agents are not used in patients with T1DM. Even though as many as 25% of patients with T1DM are overweight and insulin resistant, the insulin-sensitizing drugs (metformin and the TZDs) have no role based on available data. Studies are actively looking at this issue.

Recommendations for insulin use have been codified in Figure 2.14 There are three basic options for the use of insulin. The regimen selected depends on clinical judgment and the patient’s wishes. Regimens include:

- once-a-day injections
- multiple doses of insulin, or
- intensive insulin therapy

**Once-a-day Insulin Injections**

Some patients with T2DM can be managed with one or two insulin injections per day. As diabetes progresses, however, and the patient’s ability to produce endogenous insulin degenerates, intensive insulin therapy will be needed. The decision to advance an insulin regimen is dictated by whether glycemic goals are achieved within the time frames indicated. Important information on starting doses of insulin and how to titrate them are shown in the algorithm in Figure 2.

**Multiple Doses of Insulin**

Health care providers should instruct patients on how to titrate insulin every 2 to 3 days. Advancing from once-a-day insulin use to multiple injections is done within 6 to 12 weeks. If patients advance to multiple doses of insulin, or start on a multidose regimen, the doses will be higher but the titration scheme is the same as for once-a-day insulin use. Patients will need to advance to intensive or physiologic insulin delivery if the glucose level is not controlled within 3 to 6 months.

**Intensive Insulin Therapy**

Intensive or physiologic insulin delivery can be achieved using continuous subcutaneous insulin infusion (insulin pump) or the new, 24-hour, basal insulin glargine in combination with the fast-acting human analogs insulin lispro or insulin aspart for bolus insulin requirements. Glargine is a true long-acting insulin. It has no pronounced peak of metabolic activity. After subcutaneous injection, there is a slow constant release of insulin over approximately 24 hours. Most patients will inject insulin glargine at bedtime; however, it can be taken in the morning or in the evening as long as it is taken the same time each day. Regardless of when insulin glargine is used, fasting glucose values are used to adjust the dose. Fasting glucose reflects basal insulin requirements, and glargine is a basal insulin. If glargine is taken at bedtime, the dose is adjusted to achieve morning self-monitored blood glucose levels of less than 100 mg/dL to 120 mg/dL. If glargine is taken in the morning or the evening, the dose is adjusted based on the self-monitored blood glucose level of the following morning.

Occasionally (less than 10% of patients), mid-morning hypoglycemia may occur. In these instances, insulin glargine is given in the morning and the problem is avoided because the person usually eats three meals per day. The cause of mid-morning hypoglycemia is unknown. It is possible that insulin glargine is released from the injection site at a different rate in some patients. Insulin glargine is packaged at a pH of approximately 4. At the injection site, the tissue pH is approximately 7 and glargine forms a large complex that slowly dissociates into available insulin. Local tissue
Figure 1. [Revision available at: http://www.dshs.state.tx.us/diabetes/PDF/algorithms/PHAEM2.PDF]
**Figure 2.** Revised 04-24-03

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**INSULIN ALGORITHM FOR TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADULTS**

**Targets**

A1c -6.5–7% (<0.5-1.0% above reference range)

FPG <110–130 mg/dL

Fasting SMBG <100–120 mg/dL

2-hr PPG <140–180 mg/dL

**Treatment Naive:**

Symptomatic;

FPG ≥260 mg/dL

**Combination Oral Agent Failure:**

A1c above target but ≤9.5–10.5%

**Combination Oral Agent Failure:**

A1c >9.5–10.5%

**OPTIONS**

(in order of preference)

1. Once-daily PM or HS Insulin
2. Multi-dose Insulin
3. Intensive Insulin

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**Once-daily Insulin Therapy (QDI)**

At bedtime (BS): Intermediate-acting insulin (IAI) (pen/vial) or Long-acting insulin (LAI) (vial) or Before supper (ACS): IAI mix with Short-acting insulin (SAI) (2:1 ratio or sliding scale) (vial) or premix 70/30 or 75/25 (pen/vial)

Starting dose: 0.1–0.25 units/kg; or 6–10 units for elderly/thin complicated patients

Escalate dose every 2–3 days to attain SMBG/FPG target values; consider HS SMBG in adjusting dose of ICS mix/premix (SAI component)

Suggested Titration Schedule:

If fasting SMBG

100–120 mg/dL + 1 unit

121–140 mg/dL + 2 units

141–180 mg/dL + 4 units

≥180 mg/dL + 6 units

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**Multi-dose Insulin Therapy (MDI)**

- **2 shots**

Split mix Intermediate-acting insulin (IAI) + Short-acting insulin (SAI) (vial) (2:1 ratio AM; 1:1 ratio PM; or SAI sliding scale)

or premix 70/30; 75/25 or 50/50 (pen/vial)

- **3 shots** (especially if nocturnal hypoglycemia)

SAI: ICS and ICS sliding scale (pen/vial)

+ IAI: ABC and ACS sliding scale (pen/vial)

Starting dose: 0.3–0.5 units/kg/day; 2/3 as ICS/LAI; 1/3 as SAI

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**Intensive Insulin Therapy (IIT) — Physiologic Insulin Delivery**

1:1 basal:bolus ratio SQ

Basal: Intermediate-acting insulin (IAI) at ABC, ACS or HS (or QID) (pen/vial); or Long-acting insulin (LAI) at HS (vial)

Bolus: Short-acting insulin (SAI) at each meal (usually Lispro/Apart) (pen/vial)

Premixed insulin dose includes:

1. Insulin to cover carbohydrate ingested
2. Additional insulin to correct for high SMBG (1 unit SAI lowers PG [mg/dL] by approximately 1500/100 TD1 for Regular, 1800/100 TD1 for Lispro/Apart)

Starting dose: 0.3–0.5 units/kg/day

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**Footnotes**

1. See Glycemic Control Algorithm for Type 2 Diabetes Mellitus in Children and Adults
2. Consider simultaneous combination of oral agent therapy
3. Combining metformin with insulin therapy has been shown to result in less weight gain and better glycemic control with lower insulin requirements
4. Continue combination oral agent therapy + sulfonylureas
5. Continue metformin (± 3rd oral agent); probably discontinue sulfonylureas
6. PCD may decide to “ease” patient with poor beta-cell reserve into insulin therapy initially with QDI

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**Abbreviations**

ABC: Before breakfast
ACS: Before supper
FPG: Fasting plasma glucose
HS: Home
IAI: Intermediate-acting insulin = NPH, Lente, or Ultralente
IAI: Long-acting insulin = Largine
PCP: Primary care provider
PPI: Postprandial plasma glucose
SAI: Short-acting insulin = Regular peak action 3-4 hrs, Lispro or Aspart (peak action 1.5 hr)
SMBG: Self-monitored blood glucose
SQ: Subcutaneous
TDI: Total daily insulin units

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differences between patients may explain why some react differently to a given dose of insulin glargine.

It is unusual to use split-dose insulin glargine regimens. It is believed that less than 2% to 3% of patients with T1DM have less than 24-hour basal coverage. An important point to remember when using insulin glargine and lispro or aspart is to maintain about 50% to 60% basal insulin and 50% to 40% bolus insulin per day. It is very easy “to become upside-down” when making insulin adjustments based on glucose records. Often, a health care worker will increase the preprandial bolus insulin because glucose values at noon, evening, or bedtime are elevated and after 1 week, glycemic control deteriorates even further. Remember to “step back” and be certain that the proper ratios of basal-to-bolus insulin are used. If control is still not achieved, then it is time for the patient to work with the diabetes educator again on nutrition and lifestyle management.

The starting dose for intensive insulin therapy is indicated in the algorithm in Figure 2. For example, if a person weighs 100 kg, about 30 units to 50 units of insulin will be needed per day. Approximately one half of the amount would be given as basal insulin, and one half would be given as bolus insulin divided before meals. The “rule of 1800” (1500 for regular insulin) is used to determine an augmentation dose of bolus insulin to cover high glucose values before meals. For example, if a person used approximately 50 units of insulin per day, the rule predicts that 1 unit of insulin will reduce the blood glucose level by about 36 mg/dL (1800 divided by 50 equals 36). Many clinicians instruct patients to use an augmentation dose in addition to the bolus dose if the blood glucose level is greater than 120 mg/dL before meals. In the example given here, the patient would take about 8 units of bolus insulin before eating and an additional 1 unit of bolus insulin for every 36 mg/dL that the blood glucose level is greater than 120 mg/dL.

Intensive insulin therapy with glargine and lispro or aspart offers advantages over the older insulin regimens based on intermediate- and short-acting insulin. The intermediate-acting insulins (isophane insulin suspension, insulin zinc suspension, and extended insulin zinc suspension) cannot achieve a steady basal state because these insulin preparations have peaks of activity. Recent data using continuous glucose monitoring sensors for more than 6 months on a group of pediatric patients with T1DM taking isophane insulin suspension revealed that glucose values of less than 40 mg/dL occurred on 27% of the nights. Glucose values less than 50 mg/dL occurred on 35% of the nights. In fact, to achieve ADA goals of fasting blood glucose values of less than 120 mg/dL, 100% of patients had glucose values of less than 60 mg/dL at some time during the night. Thus, to achieve ADA goals for fasting blood glucose values, all patients are sentenced to early morning hypoglycemia. A strong argument can be made to use the basal insulin glargine because it has no pronounced peak metabolic activity and hypoglycemia is less common. The short-acting regular insulin has some definite limitations. Its peak of activity occurs at 3 to 4 hours, which is at least 1 to 2 hours after postprandial glucose spikes.

**Postprandial Glucose Control**

Control of postprandial glucose is believed to be important. Data from several studies including the Funagata Diabetes Study, the Diabetes Intervention Study, the Whitehall and Paris Perspective, and the DECODE suggest that postprandial glycemic excursions are an independent risk factor for death after a myocardial infarction. Further, there exist data to show that FPG and A1c measurements do not accurately reflect total glycemic control. The Third National Health and Nutrition Examination Survey (NHANES III) reported that of patients with an A1c of less than 6.0%, 67% had postprandial glucose values greater than 200 mg/dL, and the average glycemic excursion was 208 mg/dL.

The average A1c value of patients with T2DM in the United States is about 8.0% to 9.0%. Of these patients, 100% have postprandial excursions greater than 200 mg/dL and the average 2-hour postprandial value is 371 mg/dL. These extreme glycemic excursions and the data suggesting their relationship with post myocardial infarction death suggest that the fast-acting human analogs should be used because their rapid onset of activity coincides with the rise in postprandial glucose level.

**Intensive insulin therapy tends to mimic physiologic insulin delivery.** To explain this, let us consider where blood glucose derives from and how it is disposed of in normal physiology. Blood glucose has two main sources. Production of hepatic glucose, which supplies blood glucose during the fasting state, is constant. The gut absorbs glucose during the fed state. Basal insulin from the pancreatic beta cells disposes of hepatic glucose production into peripheral tissues while fasting.

Bolus insulin production actually occurs in two phases: the first phase occurs within several minutes of eating. It is a short, rapid burst of insulin that circulates directly to the liver. The first-phase insulin response is a signal that turns off hepatic glucose production. The second phase occurs about 15 minutes after beginning to eat and tapers back to baseline levels within 1 to 2 hours. The second-phase insulin response regulates glucose disposal into peripheral tissues during the fed state. One of the earliest changes that occurs in the prediabetic state is the loss of the first-phase insulin response. Patients with fasting glucose values between 100 mg/dL and 114 mg/dL have lost 50% of the first-phase response. Patients with glucose levels greater than 115 mg/dL have essentially no first-phase response and are similar to those who have T2DM.

An absent first-phase insulin response, an insufficient second-phase insulin response, and low basal insulin production partially explain why patients with diabetes have high blood glucose levels. They cannot dispose of basal glucose when fasting, and they receive a “double whammy” (gut and liver glucose) when eating. The purpose of using insulin glargine and fast-acting human insulin analogs is to address the basal and bolus insulin defects in diabetes. Hepatic glucose production is essentially constant, so a basal insulin with constant activity is required to regulate basal glucose.

Insulin glargine delivers usable insulin in an extremely linear fashion and appears to be almost as good as an insulin pump. It closely mimics physiologic basal
insulin in the normal state. Insulin lispro and insulin aspart have an onset of action that is detectable within 3 to 5 minutes. These very fast-acting insulins almost approximate a first-phase response to shunt off hepatic glucose production. Their short duration is similar to the normal second-phase insulin response. Thus, the kinetics of these insulins explains why glargine is used once a day and lispro and aspart are used before meals.

Patients may be reluctant to start therapy with these newer insulins because they require four injections a day. Acceptance becomes a minor issue, however, when patients realize the lifestyle flexibility that these insulins afford and the degree of glycemic control that can be achieved with less hypoglycemia. Insulin glargine can be administered anytime as long as it is the same time each day. No lifestyle adjustments are needed between the weekdays and the weekends, and rotating work shifts present no problems. The timing of meals is no longer dictated by the 4- and 8-hour peaks of short- and intermediate-acting insulins.

Comment
It is interesting to look back over the decades of insulin management of diabetes. When regular insulin was the only type available, patients routinely used four to six injections per day. One could argue that the introduction of intermediate-acting insulins and the fixed-mix preparations in the 1950s was a great step backward. It allowed patients to survive on two injections a day, but at the expense of poor glycemic control and extreme glycemic excursions.

The new recombinant basal and bolus insulins offer much. Allergic reactions are rare, hypoglycemia is less common, the postprandial glucose level is controlled, and A1c measurements of 5.0% to 6.0% are expected and routinely attained.

References