A Real-World Approach to Insulin Therapy in Primary Care Practice

Irl B. Hirsch, MD; Richard M. Bergenstal, MD; Christopher G. Parkin, MS; Eugene Wright, Jr., MD; and John B. Buse, MD, PhD

Type 2 diabetes is a progressive disease characterized by relentless deterioration of pancreatic β-cell function.[1] With the increasing incidence of type 2 diabetes, especially among younger individuals who will live longer with their disease, more patients will develop severe insulin deficiency and require insulin replacement. Because primary care providers see the vast majority of patients with type 2 diabetes, they may soon find themselves overwhelmed with insulin-requiring patients.

This article provides some practical guidelines for initiating insulin therapy in primary care practice. It is important to remember, however, that these are general guidelines and that management should be individualized for each patient.

WHY INSULIN THERAPY?

Some primary care providers may be apprehensive about using insulin in patients with type 2 diabetes. Wallace and Matthews[2] have gone so far as to suggest that patients and providers have often "colluded in implicit and unspoken contracts to continue oral agents for as long as possible."

Concerns about hypoglycemia and patient willingness and/or ability to inject insulin are good reasons why many providers may approach insulin therapy with caution. Compounding this reluctance is the perception that insulin therapy is too complex to manage in a busy primary care practice; prescribing information provided by manufacturers has been somewhat vague regarding initial dosing and titration.

Because of these factors, providers may delay in making the necessary transition from oral agents to insulin. Indeed, recent evidence suggests that the hemoglobin A_{1c} (A1C) result that triggers glucose-lowering action is ≥ 9%.[3] This is unfortunate because numerous studies have shown that excellent glycemic control can be achieved with insulin therapy in patients with type 2 diabetes.[4–7] Moreover, there is an increasing body of evidence showing that early and effective intervention with insulin is more important than had been previously believed.[8–10]

Early and Aggressive Intervention Matters

Insulin is considered the most effective treatment for lowering extremely high glucose. This is important because inhibition of glucotoxicity may be beneficial in preserving functional β-cell mass.[1] Oral agents do not work as quickly or lower glucose enough to effectively address glucotoxicity in many patients. For example, patients treated with sulfonylureas show a decrease in fasting glucose of only 60–70 mg/dl; the A1C value will decrease by 1.5–2.0 percentage points.[11,12]

New data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study highlight the importance of early intervention to aggressively lower glucose.[8] The EDIC study is an ongoing effort that follows the cohort from the Diabetes Control and Complications Trial (DCCT).[13] In the EDIC study, glycemic levels no longer differed substantially between the two original DCCT treatment groups at 7 years. However, subjects who had been intensively treated during the DCCT showed significant decreases in risk for nephropathy and retinopathy compared with subjects from the conventional treatment arm. In other words, the benefits of 6.5 years of intensive treatment during the DCCT have extended well beyond the time of intensive therapy.

Insulin May Have a Protective Quality

Insulin therapy may actually protect against endothelial damage. Observational and interventional evidence consistently indicates that glycemic control with insulin therapy in the hospital setting can improve clinical outcomes.[14–17] Malmberg et al.[14] demonstrated that the unfavorable long-term prognosis for myocardial infarction could be improved by insulin treatment. In that study, diabetic patients who received insulin infusion immediately within 24 hours of myocardial infarction, followed by multidose subcutaneous insulin treatment for at least 3 months, showed a significantly lower mortality rate (19%) at 1 year compared with subjects who received standard treatment (26%), which generally included sulfonylurea therapy.

New Insulin Analogs More Closely Match Normal Physiology

New insulin analogs (rapid and long acting) closely match normal physiology.[18–20] Rapid-acting insulin analogs, such as insulin aspart and insulin lispro, produce higher serum insulin levels earlier and have a shorter duration of action than regular human insulin. This results

in lower postprandial glucose excursions and shorter durations of postprandial hyperglycemia, with significantly reduced incidence of severe hypoglycemia in patients with type 2 diabetes.[18,19] Additionally, studies that have looked at the effects of rapid-acting insulin analogs combined with intermediate-acting insulins (free-mixed and premixed preparations) in patients with type 2 diabetes have shown improved postprandial glucose control with reduced hypoglycemia.[21–23]

New Evidence Links Glucose Excursions to Cardiovascular Risk

Reducing postprandial glucose excursions is particularly important in light of new data that show a relationship between postprandial hyperglycemia and atherosclerotic risk. A recent study from Esposito et al.[10] demonstrated that reduction of postprandial hyperglycemia in patients with type 2 diabetes is associated with carotid intima-media thickness (CIMT) regression; CIMT is a clinical marker for atherosclerosis. Recent data from Ceriello et al.[9] showed that postprandial hyperglycemia is accompanied by endothelial dysfunction in patients with type 2 diabetes and that rapid-acting insulin at mealtime improved endothelial function. Earlier reports from Ceriello et al.[24] suggest that postprandial hyperglycemia and hypertriglyceridemia induce endothelial dysfunction through oxidative stress. Other studies support the link between postprandial glucose excursions and atherosclerotic risk.[25–28]

Chiasson et al.[29] showed that addressing postprandial hyperglycemia using an α-glucosidase inhibitor actually delayed progression from impaired glucose tolerance to type 2 diabetes and was associated with a significant reduction in combined cardiovascular events. This is not a recommendation to initiate nonapproved pharmacological therapy in patients with impaired glucose tolerance. However, a significant body of evidence strongly supports the rationale for initiating therapy to achieve glycemic control in patients with type 2 diabetes much earlier and much more aggressively.

Patients Will Eventually Need Insulin Therapy

As stated earlier, type 2 diabetes is a progressive disease in which β-cell function deteriorates. Findings from the U.K. Prospective Diabetes Study (UKPDS) showed that deterioration in β-cell function occurred in the diet-only treatment group as well as in patients treated with sulfonylureas or metformin, suggesting that neither of these agents slowed the rate of decline.[30] The UKPDS also showed that even basal insulin (ultralente) did not slow β-cell deterioration.[30] Another study found that ~ 30% of patients initially treated with a sulfonylurea drug have a poor response; the remaining 70% experience a failure rate of ~ 4–5% per year.[31] It is, therefore, reasonable to conclude that most patients with type 2 diabetes will eventually need exogenous insulin.

Unfortunately, insulin therapy too often is used as a "punishment" for above-target hyperglycemia. A better approach would be to explain to patients early in the course of their disease, instead of at the end, the natural history of insulin deficiency in type 2 diabetes.[2]

WHO SHOULD BE STARTED ON INSULIN?

Initiating therapy with oral agents is a reasonable approach to take with most patients, the exception being patients with extreme hyperglycemia (fasting plasma glucose > 250 mg/dl).[32] These patients require insulin, even basal-bolus insulin therapy, to lower glucose levels. Otherwise, starting with oral therapy can be very effective, especially in patients with a short duration of diabetes and, thus, relatively adequate β-cell function. However, clinicians often wait too long to move patients from oral therapy to insulin.[33,34] In the UKPDS, only 33% of patients treated with metformin and sulfonylurea had an A1C < 7% after 3 years of treatment.[35]

When determining whether a patient should be put on insulin therapy, it is helpful to look to the guidelines for glycemic control. The American Diabetes Association (ADA)[36] and American College of Endocrinology (ACE)[37] publish goals for A1C, postprandial glucose, and fasting/preprandial glucose (Table 1). Most patients who are unable to achieve these goals using oral agents are candidates for insulin therapy. Table 2 lists the more commonly used insulins, along with information about their peak activity.

The key to making this determination is timely (preferably weekly) titration of dosages until either glucose targets are met or maximum effective dosages fail to achieve target levels. For example, weekly titration of sulfonylurea dosages, in combination with daily fasting glucose data (provided by the patient), will show whether monotherapy with sulfonylurea can provide adequate glycemic control. If not, the addition and timely titration of a second agent (metformin or a thiazolidinedione) over the next 2 months, along with continued blood glucose monitoring, will show whether combination oral therapy can provide adequate glycemic control. If not, insulin therapy is clearly warranted and should be promptly initiated (Figure 1).

Although it may be tempting to add a third oral agent, clinicians must consider the added cost and potential side effects associated with triple oral therapy. A recent study by Schwartz et al.[38] showed that a regimen of premixed insulin in combination with metformin was as effective as but much less expen-

Table 1. Goals for Glycemic Control

	ADA	ACE
A1C (%)	< 7	≤ 6.5
Fasting/ preprandial* (mg/dl)	90–130	< 110
2-hour postprandial (mg/dl)	< 180†	< 140

*Plasma equivalent.
†Peak postprandial (~ 1 hour).

Table 2. Onset, Peak, and Duration of Insulins

Insulin*	Onset	Peak	Effective duration
Rapid-acting	5–15 minutes	30–90 minutes	< 5 hours
Aspart			
Lispro			
Short-acting	30–60 minutes	2–3 hours	5–8 hours
Regular			
Intermediate (basal)	2–4 hours	4–10 hours	10–16 hours
NPH			
Long-acting (basal)	2–4 hours†	No peak	20–24 hours
Glargine			
Premixed			
75% NPL/25% lispro	5–15 minutes	Dual	10–16 hours
70% APS/30% aspart	5–15 minutes	Dual	10–16 hours
70% NPH/30% regular/NPH	30–60 minutes	Dual	10–16 hours

*Assumes 0.1–0.2 units/kg/injection. Onset and duration may vary significantly by injection site.
†Time to steady state.
Adapted from DeWitt DE, Hirsch IB: Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 289:2254–2264, 2003

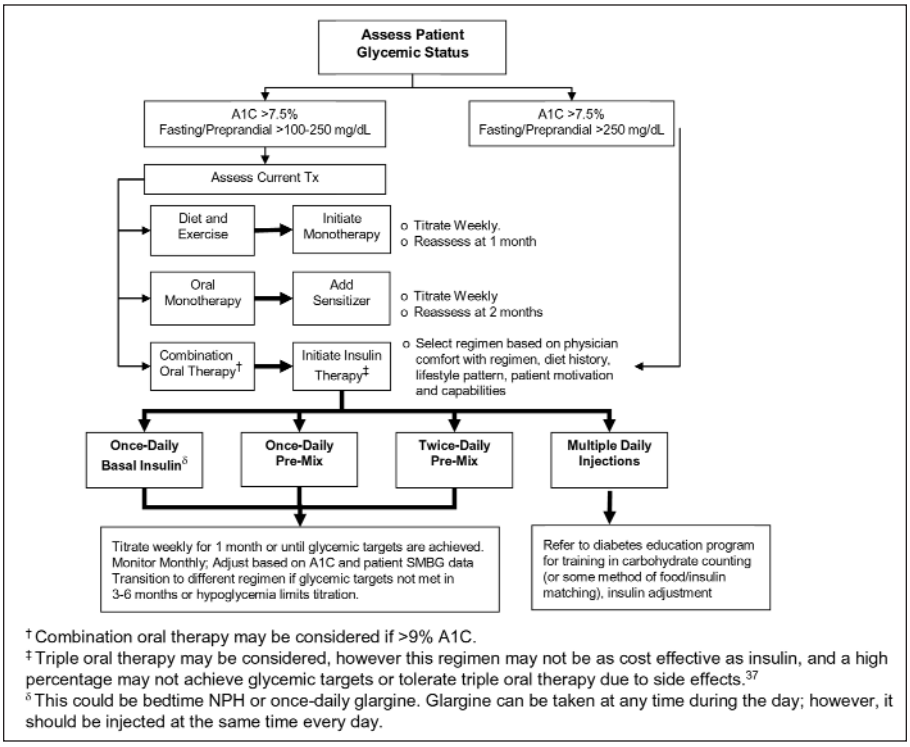


Figure 1. Algorithm for initiating insulin therapy.

sive than triple oral therapy; a high percentage of subjects (16.3%) from the triple oral agent treatment group did not complete the regimen because of a lack of efficacy or side effects.

HOW TO START PATIENTS ON INSULIN

Starting patients on insulin does not have to be difficult. This section presents an approach that takes the uncertainty and complexity out of initiating insulin therapy in patients with type 2 diabetes. Figure 1 provides an algorithm for transition from oral therapy to insulin.

Match the Regimen to the Patient

A basal-bolus regimen—glargine with rapid-acting insulin analogs at each meal—is the ideal regimen in terms of physiological action and overall glycemic control. However, many patients are reluctant to start with a basal-bolus insulin regimen. Furthermore, basal-bolus insulin management requires not only motivation of both patient and provider, but also comprehensive training in carbohydrate counting (or some method of food/insulin matching) and insulin adjustment. Therefore, it is important to match the insulin regimen to the individual needs, concerns, and capabilities of each patient.

Patients who are reluctant to do basal-bolus management initially often make the transition to multiple daily injection (MDI) regimens after gaining confidence in their ability to safely and effectively use insulin through less intensive regimens. Table 3 presents common

Table 3. Patient-Based Insulin Regimens

Basal-Only Insulin

A1C:	> 7.5–10%
Medication:	Oral medications adequately control postprandial glucose excursions
Pattern:	High fasting glucose with minimal glucose rise during the day
Diet history:	Small, regular meals (large meals will result in postprandial hyperglycemia)
Lifestyle:	Reluctance to do MDI, requires oral agents
Monitoring:	Fasting

Once- or Twice-Daily Premixed Insulin

Rapid-Acting Analog/Intermediate-Acting

A1C:	> 7.5%
Medication:	Oral agent failure (maximum tolerated dosages, contraindications, cost issues)
Pattern:	Any fasting glucose; glucose rises during the day
Diet History:	Large suppers/small lunches
Lifestyle:	Consistent daily routine, reluctance to do MDI
Monitoring:	Fasting and presupper (if insulin is administered twice daily)

Regular/NPH

A1C:	> 7.5%
Medication:	Oral agent failure (maximum tolerated dosages, contraindications, cost issues)
Pattern:	Any fasting glucose; glucose rises during the day
Diet history:	Isocaloric meals or larger lunches
Lifestyle:	Consistent daily routine, reluctance to do MDI
Monitoring:	Fasting and presupper (if insulin is administered twice daily)

Basal-Bolus (MDI)

A1C:	> 7.5%
Pattern:	Regimen can be matched to any pattern to achieve glycemic control
Diet history:	Regimen can be matched to any diet to achieve glycemic control
Lifestyle:	Erratic schedule, motivated to achieve tight glycemic control
Monitoring:	Frequent blood glucose monitoring (minimum before meals and bedtime)

insulin regimens based on patient clinical status and lifestyle characteristics.

Although regimens for once-daily glargine and once-daily and twice-daily premixed insulin are listed, it is important to note that recent studies comparing once-daily regimens to twice-daily regimens have demonstrated significant differences between the two approaches.[39–41]

One study showed that twice-daily premixed insulin (25% lispro/75% NPL) provided lower A1C levels compared with once-daily glargine when patients were randomized to one or the other insulin regimen in addition to existing metformin therapy[39] Results also showed a smaller rise in postprandial glucose levels and a higher proportion of patients achieving an A1C of ≤ 7.0% on twice-daily premixed therapy. In one study, there was a slight increase in overall hypoglycemia with no increase in nocturnal hypoglycemia,[39] whereas another study showed no difference in overall hypoglycemia with less nocturnal hypoglycemia in the premix group.[40] A third study showed similar findings regarding overall hypoglycemia.[41] In short, no definitive differences in hypoglycemia were consistently seen in these studies.

When postprandial glucose is not adequately controlled by combination therapy using basal insulin and oral agents, a twice-daily regimen using a premixed insulin preparation (prebreakfast, presupper) is preferred. Clinicians can start patients on once-daily injections at the evening meal and add the second injection as needed. Rapid-acting analog premixed insulin is an option if the patient eats small lunches or misses lunch regularly. Although no definitive studies have looked at this issue, the authors agree that for individuals eating large lunches (e.g., > 40% of their total daily calories), a better premix insulin would be 70% NPH/30% regular insulin. The problem with this regimen, however, is that the lunchtime meal needs to be consumed at about the same time each day to avoid hypoglycemia.

Basal-bolus insulin therapy may be required for patients with glucose toxicity (fasting plasma glucose > 250 mg/dl).[42] Basal-bolus insulin therapy can be continued or modified after glucose returns to near-normal levels. Additionally, basal-bolus insulin management should be presented as the next option if patients are unable to achieve targets with a premixed insulin regimen. This will be the rule for patients with more severe insulin deficiency.

Start Low and Titrate Steadily

A common starting dose for insulin therapy in patients with type 2 diabetes is 0.15 units/kg body wt/day;[42] however, because > 90% of patients with type 2 diabetes are insulin resistant,[43] significantly higher doses are often required to achieve glycemic targets.[39-41,44]

The Treat-to-Target study[44] used a starting dose of 10 units/day with glargine or human NPH at bedtime; mean daily dosages at end point adjusted for body weight were 0.48 units/kg for glargine and 0.42 units/kg for NPH in those patients who were maintained on one or two oral agents throughout the study. This is equivalent to ~ 40 units/day in an average 200-lb patient. A study of premixed insulin in patients on oral agents initiated insulin therapy with a dose of 6 units/day; however, the average dosage at 28 weeks was > 75 units/day (0.85 units/kg/day), with no major hypoglycemic episodes reported.[41]

The differences in average dosages at end point reported in these studies resulted from differences in baseline A1C levels, durations of diabetes, and

overall levels of insulin resistance in the study subjects. Nevertheless, these studies show 10 units/injection to be a safe starting dose for once-daily and twice-daily insulin regimens (Table 4).

It is important to note that although glargine can be taken at any time during the day, it should be injected at the same time every day. Patients should document all results from self-monitoring of blood glucose (SMBG) and insulin doses in their logbooks when starting or adjusting insulin. Glucose meter downloading is another excellent tool for review of SMBG data.[45]

Monitor and Adjust Therapy Until Targets are Achieved

Although insulin is the most effective treatment for lowering glucose, a recent national study showed that only half of patients with type 2 diabetes who are treated with insulin achieve an A1C < 7%.[46] To be successful, insulin therapy requires timely and appropriate titration of dosages. Table 5 presents a titration schedule that can be used with once-daily and twice-daily regimens to make safe and timely insulin adjustments.

Working with this schedule, patients measure blood glucose once or twice daily (prebreakfast, presupper) depending on their regimen. Based on these blood glucose data reported by the patient, the clinician can then make stepwise adjustments in response to the average glucose values. Prebreakfast dosage adjustments are based on presupper glucose results, whereas presupper dosage adjustments are based on prebreakfast glucose values.

For example, in a patient on 10 units of premixed insulin twice daily who reports prebreakfast glucose values ranging from 148 to 175 mg/dl over the past 3–7 days, the appropriate adjustment would be an additional 4 units of insulin before supper.

Another key aspect of insulin titration is timely adjustment. As with oral therapy, clinicians often wait too long to make adjustments in insulin dosages, allowing excessive glycemic exposure to persist for months (or years, in some cases). A major obstacle to timely insulin adjustment is primarily the logistics of communicating with the patient. Table 6 presents some options for patient follow-up that may expedite achieving glycemic targets on timely basis. Diabetes education is a crucial aspect of patient care and is recommended for all patients, particularly those who are self-adjusting their insulin dosages.

If patients are not at goal after 3–6 months of therapy or if recurrent hypoglycemia limits titration, consider changing the regimen. Table 7 presents strategies for making this transition.

When assessing the need to change regimens, it is important to understand

Table 4. Starting Dosages

1 × Premix	10 units (presupper)
2 × Premix	10 units (prebreakfast), 10 units (presupper)
1 × Basal	10 units (bedtime)
MDI	Individualized*

*Patients with type 2 diabetes seldom start insulin on an MDI regimen. Dosages should be based on the current insulin regimen. Additionally, consider referral to a certified diabetes education program for training in carbohydrate counting and insulin adjustment.

Table 5. Dosage Titration for Once-Daily or Twice-Daily Insulin Regimens

Most Values (during last 3–7 days)	Dosage Change
< 80 mg/dl	–2 units
80–109 mg/dl	No change
110–139 mg/dl	+2 units
140–179 mg/dl	+4 units
≥ 180 mg/dl	+6 units

Adjust prebreakfast dose based on presupper/evening value.
Adjust presupper (premixed)/bedtime (basal) dose based on prebreakfast/morning value.
DO NOT increase dose if hypoglycemia (< 70 mg/dl) or symptoms are present.

Table 6. Options for Patient Follow-Up

1. **Patient visit**
   - First month: Patient visits physician once per week.
   - Thereafter until glycemic targets are achieved: Patient visits physician or sends blood glucose monitoring data weekly to physician via phone, fax, or e-mail. Physician/nurse responds with instructions for dosage adjustment.
2. **Phone, fax, e-mail**
   - First month: Patient sends blood glucose monitoring data weekly to physician via phone, fax, or e-mail. Physician/nurse responds with instructions for dosage adjustment.
   - Thereafter until glycemic targets are achieved: Patient continues to send blood glucose monitoring data weekly. Physician/nurse (by protocol) responds with instructions for dosage adjustment.
3. **Patient self-adjustment**
   - First month: Patient monitors blood glucose, adjusts insulin dosage as needed, and sends monitoring and dosage adjustment data weekly to physician via phone, fax, or e-mail. Physician/nurse (by protocol) responds with instructions for dosage adjustment.
   - Thereafter until glycemic targets are achieved: Patient continues to send blood glucose monitoring and insulin adjustment data to physician weekly. Physician/nurse (by protocol) responds with instructions for dosage adjustment.

Table 7. Transition From One Regimen to Another

Current 1 × Basal → New 2 × Premix
- Divide total daily dose in half. Give prebreakfast and presupper premix insulin. The new regimen should be started 18–24 hours after last basal dose was given.
- Titrate to goal based on SMBG data and diet history. The largest meal requires a larger proportion of insulin.
- Reduce total dose by 20% if there is recurrent hypoglycemia.

Current 1 × Premix → New 2 × Premix
- Divide total daily dose in half. Give prebreakfast and presupper.
- Titrate to goal based on SMBG data and diet history. The largest meal requires a larger proportion of insulin.
- Reduce total dose by 20% if there is recurrent hypoglycemia.

Current 1 × Basal Only → Add Rapid-Acting Insulin at Largest Meal*
- Give 10% of total daily dose as rapid-acting analog at largest meal.
- Reduce basal dose by 10%.

Current 2 × Premix → MDI†
- Divide total daily dose in half.
- Initial basal insulin dose = total daily dose/2 × 80%.
- Initial prandial insulin dose = half of total daily dose × percentage of estimated calories for each meal

* This regimen serves as a transition to MDI therapy.
† Example: Patient is currently on 60 units total daily dose of premix insulin (30 units twice daily) and eats ~ 20% of total daily calories at breakfast, 20% at lunch, and 60% at supper. The new regimen would be 24 units of basal insulin with 6 units of rapid-acting insulin at breakfast, 6 units at lunch, and 18 units at supper.

and consider the impact of fasting glucose and postprandial glucose on overall glycemic control. Monnier et al.[47] recently published findings that showed a variable relationship between fasting and glucose based on current A1C levels. As shown in Figure 2, the report revealed that the relative contribution of fasting glucose to overall glycemia is ~ 70% in patients with an A1C of > 10.2%; the contribution of fasting glucose decreases as A1C levels decrease.

Knowing the relative contribution of fasting and postprandial glucose to A1C allows clinicians to make more informed decisions about therapy. For example, if a patient's A1C is at 7.5%, adjustment should focus on lowering postprandial glucose; adding basal insulin will not directly address postprandial hyperglycemia. Although the addition of basal insulin will improve the overall A1C, as shown in the Treat-to-Target study,[44] it will not lower the degree of postprandial excursions. Only meal plan modification or prandial insulin will address this issue. Figure 3*A* illustrates how addressing fasting glucose can initially lower fasting levels and even improve postprandial excursions by reducing glucotoxicity and thus improving β-cell function. However, once fasting glucose levels are normalized, increasing the basal dosage will not adequately address the remaining postprandial hyperglycemia (Figure 3*B*). Therefore, a regimen that addresses both fasting and postprandial hyperglycemia is needed (Figure 3*C*).

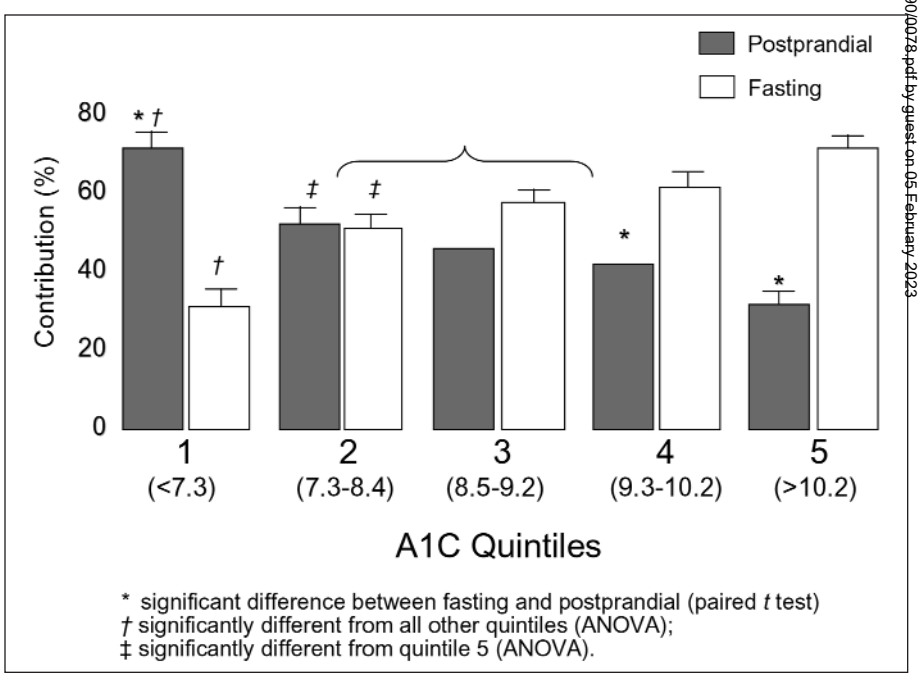


Figure 2. Relative contribution of fasting and postprandial glucose to A1C. Adapted from Monnier et al.[47]

CONCLUSION

Insulin therapy in the treatment of type 2 diabetes offers significant advantages in efficacy and outcomes. However, unfounded fear of hypoglycemia and uncertainties regarding initial dosage and titration have been key obstacles for many providers when making the decision to initiate insulin treatment in their patients with type 2 diabetes.

Given the progressive nature and increasing incidence of type 2 diabetes, more patients will be faced with severe insulin deficiencies in their lifetimes. It is hoped that the information and recom-

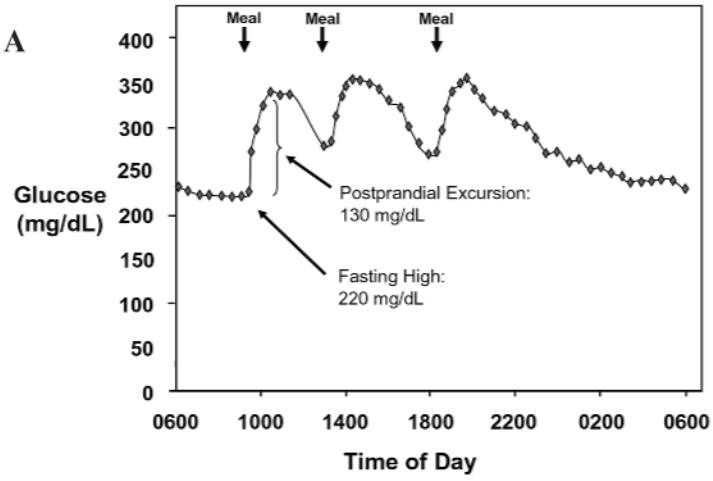
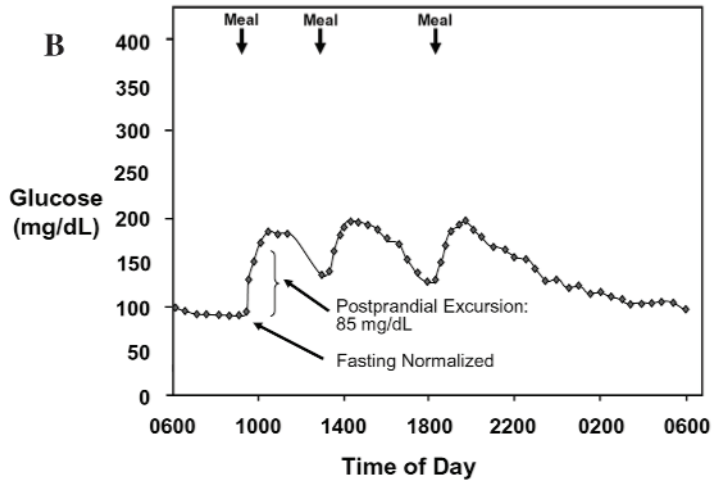
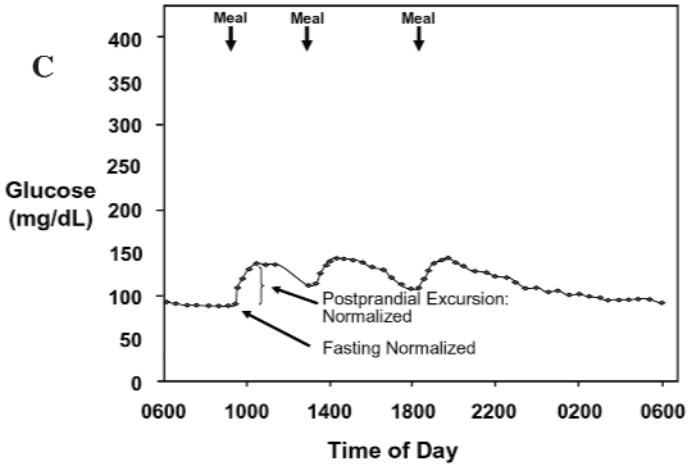


Figure 3 (A). Elevated fasting glucose with large postprandial glucose excursion.



(B). Use of basal insulin normalizes fasting glucose and reduces postprandial glucose excursions by reducing glucotoxicity



(C). Use of basal and mealtime insulin addresses fasting and postprandial hyperglycemia.

mendations provided in this article will help primary care providers become more effective in their management of patients with type 2 diabetes.

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Irl B. Hirsch, MD, is a professor of medicine in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington Medical Center in Seattle. Richard M. Bergenstal, MD, is executive director of the International Diabetes Center and a clinical professor at the University of Minnesota, both in Minneapolis. Christopher G. Parkin, MS, is a medical writer and consultant to professional medical organizations and healthcare companies and president of CGParkin Communications in Carmel, Ind., Eugene E. Wright, Jr., MD, is medical director of Primary Care and

Specialty Practices of Cape Fear Valley Health System in Fayetteville, N.C. John B. Buse, MD, PhD, is an associate professor at the University of North Carolina School of Medicine in Chapel Hill, where he is the division chief of General Medicine and director of the Diabetes Care Center. He is also an associate editor of Clinical Diabetes.

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