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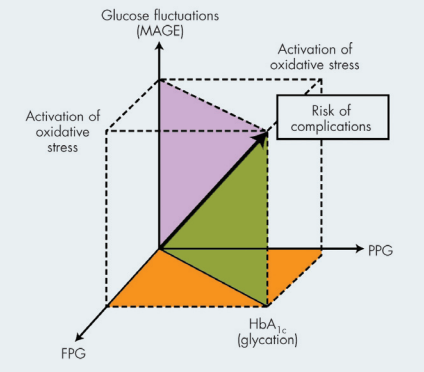
Current Issues in the Management of Type 2 Diabetes



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Introduction

Current Issues in the Management of Type 2 Diabetes

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The threat of diabetes looms larger than ever as obesity rates rise because of the availability of low-cost "junk" foods and increasingly sedentary lifestyles. The incidence and prevalence of diabetes are high and rising: recent data indicate that the disease has been diagnosed in 23.6 million people in the United States (7.8% of the population), with 1.6 million new adult cases each year.[1]

Despite effective treatments, approximately 44% of patients still fail to achieve the American Diabetes Association target of hemoglobin A_{1c} levels lower than 7%.[2,3] The need to educate patients about diabetes risk factors, natural history, and treatment options is thus greater than ever, but at a time when health care providers are increasingly stretched for time and resources. We cannot ignore the fact that while current diabetes treatments can delay the onset and progression of the disease, their limitations may also reduce their acceptability. Novel therapies that address these shortcomings are urgently needed.

In this supplement, we summarize the strengths and limitations of current diabetes treatments, including their modes of action, pharmacokinetic properties, and adverse-event profiles, and we explore the contribution of health care practitioner and patient behaviors to suboptimal diabetes management. The primary focus is on type 2 diabetes, although there is discussion of type 1 disease where appropriate. The phenomenon of clinical inertia—and the means of addressing it—is discussed, as are educational initiatives that have been shown to enhance treatment understanding and adherence among patients.

Discussion of the limitations of existing treatments naturally leads to discussion of what newer diabetes treatments have to offer. We present clinical trial data for insulin analogs, demonstrating their ability to more closely match the nondiabetic insulin profile and thus provide better glycemic control with reduced incidence of adverse effects and greater lifestyle flexibility than traditional human insulin formulations. Important insulin analog trials are summarized. These include the original treat-to-target trials of insulin glargine and insulin detemir that have demonstrated how ambitious titration algorithms can be used to tolerably achieve clinically important improvements in the glycemic control of type 2 diabetes using simple regimens. Also discussed is the **T**reat to **T**arget in **T**ype **T**wo (4-T) study, which has compared 3 different kinds of insulin analog used as initial insulin therapy in type 2 diabetes; studies examining the feasibility of patient-driven titration; and large-scale, multinational observational studies that have assessed the clinical impact of insulin analogs in type 1 and type 2 diabetes. The authors explore how intensive diabetes education programs, in conjunction with novel therapies and insulin pens, can facilitate accurate insulin dosing and delivery and treatment adherence. They emphasize the need to initiate and intensify diabetes treatment as soon as glycemia is no longer adequately controlled using existing treatment strategies. Finally, we present case studies that illustrate how an individualized approach to treatment selection and intensification can help patients improve their glycemic control and reduce cardiovascular risk while offering a sense of empowerment and control over their disease and its day-to-day management.

The need for prompt recognition of inadequately controlled glycemia and the logical next step—initiating or intensifying treatment, using insulin when necessary—cannot be overstated. By following evidence-based guidelines and by using the most effective treatment strategies available in a timely manner, we can offer patients the best possible clinical outcomes.

Thank you for joining me in this endeavor. ■

Dr Edelman is professor of medicine at the University of California, San Diego.

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Type 2 Diabetes: Limitations of Current Therapies

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ABSTRACT: Type 2 diabetes is a chronic disease associated with numerous microvascular and macrovascular complications. It affects millions of persons worldwide, posing an enormous socioeconomic burden. A growing body of evidence shows that comorbidities are greatly reduced when adequate glycemic control is achieved. Unfortunately, despite the variety of therapies currently available, the majority of patients do not achieve glycemic goals. Recent evidence demonstrating that diabetes progression can be stopped or even reversed with early and aggressive intervention, and the advent of therapies that address several of the mechanisms of diabetes pathophysiology, offers much promise for the future. This review article will identify the direct and indirect limitations of current type 2 diabetes therapies, and will explore new ways in which these limitations can be overcome.

The prevalence of type 2 diabetes is relentlessly increasing as a result of today's more sedentary lifestyles and increased obesity. In 2000, an estimated 171 million people worldwide had diabetes, and the number is projected to reach 366 million by 2030,[1] resulting in high morbidity and a large economic burden.

The pathophysiology of type 2 diabetes is progressive, characterized by decreased insulin sensitivity, deteriorating β-cell function,[2] and decreased incretin function.[3] Decreased insulin function leads to chronic hyperglycemia (during fasting and postprandial periods) and acute glycemic fluctuations. These may be associated with microvascular and macrovascular complications caused by excessive protein glycation and activation of oxidative stress (**Figure**).[4] The ultimate goal of type 2 diabetes treatment, therefore, should be to reduce all the components of dysglycemia.

CAN DISEASE PROGRESSION BE HALTED?

Type 2 diabetes is typically managed with rigorous medical therapy and a stepwise approach, including initial lifestyle modifications, the addition of oral antidiabetic drugs (OADs), and the addition of insulin. Fortunately, early educational intervention can halt or even reverse disease progression. For example, Tuomilehto and colleagues[5] and the Diabetes Prevention Program Research Group[6] investigated the effect of intensive nutrition and exercise counseling on the progression from impaired glucose tolerance (IGT) to type 2 diabetes. A 58% relative reduction in the progression to diabetes was observed in both studies compared with standard diet and exercise programs.

Programs that promote a healthier diet and more active lifestyle can be very successful in helping patients achieve weight loss in the short term. Patients enrolled in such programs lose approximately 10% of their body weight over 20 to 26 weeks, which can provide significant reductions in hemoglobin A_{1c} (HbA_{1c}) levels (about 1% to 2%) and improvement in cardiovascular disease risk factors.[7] Unfor-

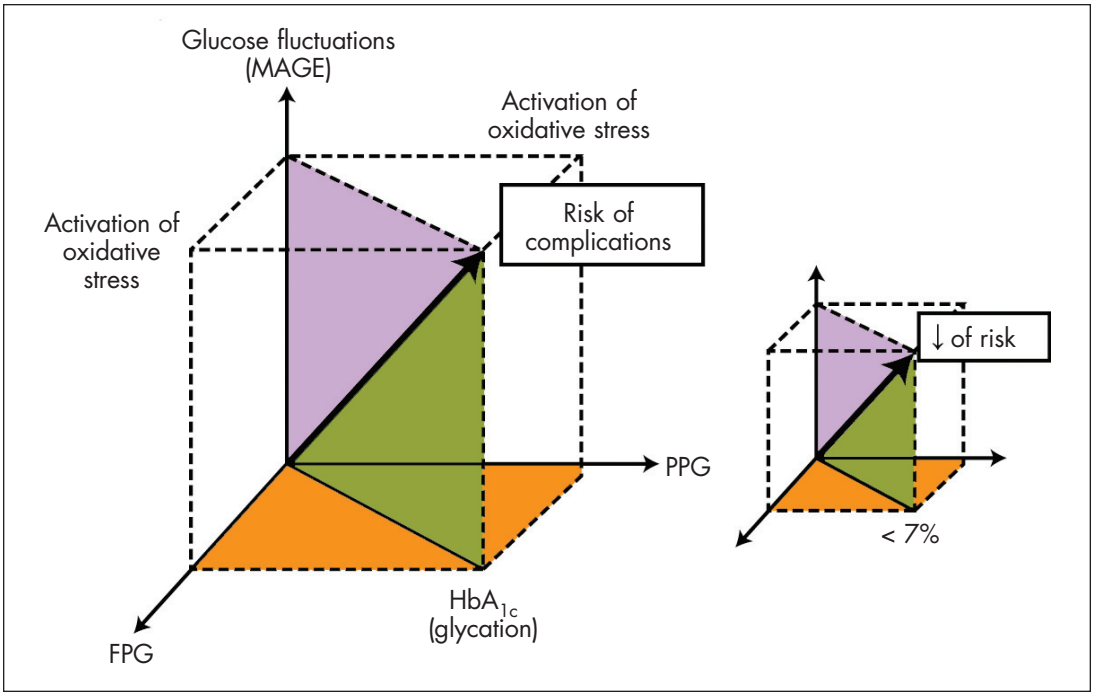

Figure – This model illustrates the pathophysiological impact of excessive glycation of proteins and activation of oxidative stress on the risk of diabetes complications (diagonal solid arrow). The contributions of the 3 components of dysglycemia—hyperglycemia at fasting (fasting plasma glucose [FPG]), hyperglycemia during postprandial periods (postprandial glucose [PPG]), and acute glucose fluctuations (mean amplitude of glycemic excursions [MAGE])—are indicated on the *x, y,* and *z* axes, respectively.

tunately, this approach alone fails to achieve adequate glycemic control within 1 year for the majority of patients. It is extremely difficult for patients to modify lifelong habits, and most will ultimately require pharmacotherapy to restore normoglycemia.[7]

Despite the potential of lifestyle modifications and early intervention to halt disease progression, the majority of patients currently have poor glycemic control, with less than 50% reaching the recommended American Diabetes Association (ADA) target of HbA_{1c} levels lower than 7%.[8,9]

CAN THERAPEUTIC LIMITATIONS BE OVERCOME?

OADs are normally introduced when lifestyle modifications fail to adequately control glycemia. They are very useful for managing hyperglycemia, especially in the early stages of disease, achieving typical HbA_{1c} reductions of 0.5% to 2.0%.[10] However, there are several limitations that prevent OADs from reaching their potential.

Direct limitations: mechanisms of action and side effects. The success of OADs is limited by their mechanisms of action, which often address the symptoms of diabetes rather than its underlying pathophysiology. OADs may also have undesirable side effects. For instance, up to 2.5% and 17.5% of sulfonylurea (SU)-treated patients experience major and minor hypoglycemia, respectively, while GI problems affect up to 63% of metformin-, 36% of thiazolidinedione (TZD)-, and 30% of acarbose-treated patients. Peripheral edema is observed in up to 26% of TZD-treated patients, and body weight increases of 2.2 to 11.0 lb (1 to 5 kg) are common with both SU and TZD therapy.[11] These side effects can have a negative impact on patient adherence to treatment, resulting in higher HbA_{1c} levels and increased risk for all-cause hospitalization and all-cause mortality.[12]

Overcoming limitations: failure of sufficiently proactive disease management. Another limitation hindering the efficacy of OADs is clinical inertia on the part of health care practitioners who delay initiation and intensification of therapy. OADs are frequently initiated too late in the progression of the disease and intensification is delayed, needlessly exposing the patient to damaging levels of hyperglycemia. For example, a retrospective observational study showed that patients with type 2 diabetes received monotherapy with metformin or an SU for 14.5 and 20.5 months, respectively, before additional treat-

ment was initiated, in spite of HbA_{1c} levels higher than 8%.[13] This is much later than recommended in the most recent American Association of Clinical Endocrinologists (AACE) road map guidelines, in which combination therapy is indicated when continuous titration of OAD monotherapy fails to achieve target HbA_{1c} levels (ie, ≤ 6.5%).[14] Although insulin is the most effective antihyperglycemic agent, its initiation is also delayed to an excessive degree. Brown and associates[13] estimated that the average patient accumulated almost 5 HbA_{1c}-years of excess glycemic burden (HbA_{1c} > 8%) from diagnosis until insulin initiation, increasing the prevalence of complications.

Clinical inertia has a negative effect on the economic burden of diabetes as well, since the direct costs of the disease increase greatly as complications develop.[15] Therefore, there is a growing consensus that a more aggressive approach to diabetes management must be implemented.[16] This approach involves prompt intensification of OADs as soon as they fail to achieve HbA_{1c} targets, and earlier initiation of combination therapy, since adding an OAD with a complementary mechanism of action can have an additive or synergistic effect on glucose control. For example, SU and metformin combination therapy has been shown to reduce HbA_{1c} levels by 1.7% in patients who were not achieving adequate glycemic control with SU monotherapy, and where increases in SU dose or switching to metformin monotherapy did not significantly reduce HbA_{1c} levels.[17] Unfortunately, OADs are unable to mitigate the inevitable and progressive β-cell decline that occurs during the natural progression of diabetes. Even if treatment is intensified promptly, 59% of patients who have had a diagnosis of type 2 diabetes for more than 10 years and 75% who have had a diagnosis for at least 20 years do not achieve adequate glycemic control with OAD therapy alone.[18]

INSULIN: LIMITATIONS AND SOLUTIONS

Currently, insulin therapy is the only medication with the proven potential to bring any patient to glycemic target at any point in the progression of the disease. It is typically prescribed after OADs have failed, and regrettably often later than is ideal. Glucose is the main stimulator of insulin secretion, and glucose levels in healthy individuals are maintained within relatively narrow limits. The physiological plasma insulin profile in healthy individuals displays low but constant insulin levels in fasting conditions, with sharp prandial peaks shortly (within 30 minutes) after meals followed by a slow return to basal levels when increased insulin secretion is no longer necessary. In order to avoid glycemic excursions, exogenously administered insulin would ideally closely mimic the healthy physiological pharmacokinetic insulin profile.

Direct limitations. Unfortunately, conventional human insulin is associated with several characteristics that limit its potential. Unmodified human insulin injected intravenously has a 17-minute half-life and a short duration of action.[19] However, when subcutaneously injected for mealtime control, human insulin has a slower onset of action and a prolonged effect compared with endogenous insulin, but must be injected 30 to 60 minutes before the meal in order to avoid postprandial hyperglycemia and between-meal hypoglycemia.

Intermediate-acting human insulin (ie, neutral protamine hagedorn [NPH]) used for basal glucose control has pronounced nonphysiological peaks in serum concentration 4 to 8 hours after injection.[20] This failure to mimic the physiological insulin profile often results in a mismatch between blood glucose and insulin peaks, predisposing the patient to hypoglycemia. Nocturnal hypoglycemia is of particular concern, since patients are unlikely to recognize the warning symptoms or wake up during an event and are thus unlikely to take any preventative action.

Two randomized trials comparing NPH insulin with the insulin analogs insulin detemir and insulin glargine, respectively, have highlighted the higher incidence of overall and nocturnal hypoglycemia associated with the nonphysiological profile of human insulins.[21,22] In these trials, the number of hypoglycemic and nocturnal hypoglycemic events, respectively, per patient-year were 16.0 and 3.3 with NPH insulin versus 8.6 and 1.5 with insulin detemir (both $P < .001$),[21] and 17.7 and 6.9 with NPH insulin versus 13.9 and 4.0 with insulin glargine ($P < .02$ and $P < .001$, respectively).[22] The high incidence of hypoglycemia associated with NPH insulin is a clear limitation of this treatment, since hypoglycemia is a recognized barrier to achieving glycemic goals.[23]

Insulin therapy is often accompanied by weight gain. Hermansen and associates[24] recently reviewed 7 trials of 20 to 52 weeks' duration in which basal insulin analogs (insulin detemir or insulin glargine) or NPH insulin were added to the existing OAD regimens of insulin-naive patients with type 2 diabetes. Weight gain was observed in all cases after insulin initiation, with reported weight increases at the end of the trials varying from 1.5 to 2.6 lb (0.7 to 1.2 kg) with insulin detemir, 4.4 to 8.6 lb (2.0 to 3.9 kg) with insulin glargine, and 3.5 to 6.4 lb (1.6 to 2.9 kg) with NPH insulin. Weight gain has been identified by patients and health care providers as a common concern prior to insulin initiation,[25] and is one of the key factors responsible for patients' resistance to insulin intensification.[26,27]

Finally, the traditional vial and syringe method of insulin administration

is associated in some cases with needle aversion, social stigma, lack of convenience, difficulty with accurate dosing and, eventually, decreased adherence to the prescribed insulin regimen.[28] Up to 25% of patients experience anxiety about self-injection, and discrepancies between the intended dose and the dose that is actually delivered can be greater than 25% in many patients.[29] Another important limitation of vial and syringe administration of insulin is the risk of needlestick injury among health care providers. In a retrospective study of nurses caring for patients with diabetes, 80% of all reported needlestick injuries were caused by disposable syringes.[30]

Indirect limitations. The limitations of conventional insulin therapy have given rise to a number of barriers to timely initiation and intensification, including physicians' unwillingness to prescribe insulin and patients' nonacceptance of insulin therapy, resulting in unnecessary exposure of the patient to hyperglycemia.[17] These issues are described in greater detail in a separate article on clinical inertia in this supplement (page S20).

Overcoming barriers to appropriate insulin use. Many patients are able to reach and sustain glycemic goals with aggressive and continual insulin dose titration,[31] and there is a growing call for earlier and more aggressive intensification of insulin as a result. For example, the most recent guidelines issued by the AACE[32] call for therapy-naive patients with HbA_{1c} levels higher than 10% to initiate insulin with either basal-bolus therapy or premixed insulin. The same approach was recommended for OAD-treated patients with HbA_{1c} levels remaining higher than 8.5%.[16] The benefits associated with newer insulin analogs (vs conventional insulin) and newer insulin pen delivery devices (vs vial and syringe) may facilitate implementation of these guidelines by reducing barriers to insulin initiation and intensification.

New insulin analogs and delivery systems. Numerous studies have shown that the new analogs, which have improved pharmacokinetic and pharmacodynamic profiles (**Table 1**), are effective in reducing HbA_{1c} levels with a lower risk of overall and nocturnal hypoglycemia compared with conventional insulins.[21,22] Insulin detemir has also been shown to consistently reduce within-subject variability in plasma glucose levels compared with NPH insulin in type 2 diabetes patients on basal-bolus therapy,[33] and this has been strongly associated with a reduced incidence of nocturnal hypoglycemia in the clinical setting.

Three-month data from the global prospective multinational observational PREDICTIVE study, which follows patients with type 1 and type 2 diabetes who were treated with NPH insulin or insulin glargine prior to the study and switched to insulin detemir, showed that after switching, the percentage of patients with type 2 diabetes who experienced nocturnal hypoglycemia decreased from 13.4% to 2.8% ($P < .001$) in association with reduced plasma glucose variability (reduced from 15.7% to 12.9% [$P < .01$]); ($r = 0.145$; $P < .001$).[34] Reduced glycemic variability could also have a beneficial effect on diabetes complications, since glycemic variability has been shown to contribute to oxidative stress by increasing superoxide production (which itself has been implicated in many of the hyperglycemia-induced mechanisms involved in the development of diabetes complications).[35,36]

Insulin detemir has also been shown to induce less weight gain than either NPH or insulin glargine.[24] In a 26-week study comparing the effect of twice-daily insulin detemir versus twice-daily NPH insulin as add-on therapy to OADs in insulin-naive patients with type 2 diabetes, weight increases of 2.6 lb (1.2 kg) versus 6.16 lb (2.8 kg), respectively, were observed.[21] Similarly, in a 52-week study comparing once-daily detemir versus once-daily glargine as add-on therapy to OADs in insulin-naive patients, weight increases of 5.1 lb (2.3 kg) versus 8.6 lb (3.9 kg), respectively, were reported.[37]

Modern pen devices for insulin delivery are easy to use, cause little or no pain, and are preferred by patients over vial and syringe,[38,39] all of which are likely to have a positive effect on patients' adherence to insulin therapy.[40] Studies comparing the dos-

Table 1 – Traditional versus analog bolus and basal insulins: key pharmacodynamic characteristics

	Insulin	Onset	Peak	Duration
Bolus	Regular	30 - 60 min	2 - 3 h	8 - 10 h
	Lispro	5 - 15 min	30 - 90 min	4 - 6 h
	Aspart	5 - 15 min	30 - 90 min	4 - 6 h
Basal	NPH	2 - 4 h	4 - 10 h	12 - 18 h
	Glargine	2 - 4 h	No peak	24 h
	Detemir	2 - 4 h	No peak	20 - 24 h

NPH, neutral protamine hagedorn.

Adapted with permission from Phillips LK, Phillips PJ. *Aust Fam Physician*. 2006.[57]

ing accuracy of pen devices versus vial and syringe have shown pens to be more accurate, particularly for the elderly and for patients delivering low insulin doses.[29] Some modern pen devices such as the NovoFine® Autocover® (Novo Nordisk) 30 gauge × 1/3-in (8-mm) (NFA) needle, a single-use product with an automatic safety lock, and the BD Autoshield™ Pen Needle (Becton-Dickinson), which has a shield that locks in place after injection, have been designed specifically to minimize the risk of needlestick injury.[41]

PATIENT EDUCATION AND DIABETES MANAGEMENT PROGRAMS

Patient education plays an important role in reducing barriers to lifestyle modifications and initiating or intensifying treatment. This can maximize the potential for improved glycemic control. It is important to stress the progressive nature of diabetes to patients at the time of diagnosis, as well as the fact that insulin may eventually be needed to achieve good glycemic control and avoid complications.[28]

Structured intensive diabetes education programs (SIDEPs) can motivate and empower patients to take control of their disease and have been associated with improved glycemic control, increased adherence to treatment, and improved acceptance of insulin.

In a study of patients with type 2 diabetes who underwent an in-patient SIDEP versus hospitalized patients aiming for glycemic control without intensive education, the group receiving intensive education had significantly improved HbA_{1c} levels, less frequent subsequent hospitalizations, and improved adherence to self-care behavior.[42]

Project Dulce also demonstrated the efficacy of nurse care management and peer education and empowerment groups in the treatment of patients with diabetes in underserved ethnic populations. Patients enrolled in the project were primarily Latino, and all had diagnosed type 1 or type 2 diabetes. After 1 year, HbA_{1c} levels, total cholesterol, LDL cholesterol, and diastolic blood pressure were significantly lower in the enrolled subjects than in a matched control group. Standards of diabetes care, knowledge of diabetes, treatment satisfaction, and culture-based beliefs were also improved.[43] These studies highlight the importance of optimum patient management and education in achieving adequate glycemic control in a clinical setting.

THE PROMISE OF INCRETIN-BASED THERAPIES

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucagon-dependent insulin-releasing polypeptide (GIP) are released in the intestine shortly after nutrient ingestion; they are responsible for mediating the "incretin effect" (ie, the enhanced insulinotropic effect observed after oral glucose administration compared with an isoglycemic intravenous challenge)[44] by inducing glucose-dependent insulin secretion. In persons with type 2 diabetes, however, there is a marked decrease in the insulinotropic effect of GIP,[45] together with probable decreased secretion of GLP-1,[46,47] which may contribute to the deficient postprandial insulin response observed in this disease.[48]

A new generation of therapies aimed at enhancing incretin action in type 2 diabetes is currently being developed, including agents that inhibit the dipeptidyl peptidase-4 (DPP-4) enzyme responsible for rapid degradation of GLP-1 (DPP-4 inhibitors: sitagliptin, alogliptin, and saxagliptin), as well as agents that are able to bind to and activate GLP-1 receptors while remaining less susceptible to DPP-4 degradation than native GLP-1 (GLP-1 receptor agonists such as exenatide and human GLP-1 analogs such as liraglutide). Exenatide is derived from a peptide found in the saliva of *Heloderma suspectum* (also known as the Gila monster). It shares only 53% of its structure with native GLP-1 and is therefore less susceptible to DPP-4 degradation than the native molecule; however, because of the lower sequence identity to human GLP-1, exenatide elicits antibody formation in about 43% of patients.[49] The clinical significance of this remains unclear.

Liraglutide, on the other hand, is a fully human protein and shares 97% of its sequence with native GLP-1, with a single amino acid substitution and the addition of an acyl side chain responsible, in part, for its extended half-life.[50] Antibody formation with liraglutide occurs in up to 12.7% of patients.[51]

Unlike the majority of traditional treatment options, incretin-based therapies address several of the mechanisms that contribute to type 2 diabetes by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner, thus reducing the risk of hypoglycemia. These agents also reduce plasma glucose levels, sometimes with clinically meaningful associated weight loss (in the case of exenatide and liraglutide) or without weight gain (in the case of DPP-4 inhibitors) (**Table 2**). Exenatide and liraglutide have the additional advantage of improving biomarkers of β-cell function.[50]

Limitations of GLP-1 receptor agonists are the associated GI side effects that typically occur at treatment inception. In particular, nausea has been reported in 40% to 50% of patients receiving exenatide 5 or 10 µg twice daily,[52] and in 7% to 40% of patients receiving liraglutide 0.6, 1.2, or 1.8 mg once daily.[51,53-56] Nausea ap-

Table 2 – Overview of selected GLP-1 receptor agonists and DPP-4 inhibitors

Drugs	HbA_{1c} reduction (%)	Route of administration	Dosing	Weight effect	Reference
GLP-1 receptor agonists					
Exenatide		Subcutaneous	BID	↓	
+Met	− 0.78				DeFronzo, 2005[49]
+SU	− 0.86				Buse, 2004[52]
+TZD+Met	− 0.98				Zinman, 2007[58]
+SU+Met	− 0.80				Kendall, 2005[59]
Liraglutide		Subcutaneous	OD	↓	
Monotherapy	− 1.14				Garber, 2009[56]
+Met	− 1.00				Nauck, 2009[60]
+SU	− 1.10				Marre, 2009[51]
+TZD+Met	− 1.50				Zinman, 2009[55]
+SU+Met	− 1.33				Russell-Jones, 2008[54]
DPP-4 inhibitors					
Sitagliptin monotherapy	− 0.94	Oral	OD	↔	Aschner, 2006[61]
Saxagliptin monotherapy	− 1.09	Oral	OD	↔	Rosenstock, 2008[62]

GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, hemoglobin A_{1c}; Met, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

pears to be transient, in most cases occurring only during the first 1 to 2 weeks of treatment. Thus, these therapeutic agents are a promising new option for the management of type 2 diabetes that can be used as first-line monotherapy and in combination with 1 or more OADs. The ADA, AACE, and European Association for the Study of Diabetes recognize the value of incretin-based therapies, and recommend their initiation when lifestyle modification and metformin are insufficient to lower HbA_{1c} to below 7%.[7]

CONCLUSION

Although type 2 diabetes is a progressive disease, evidence shows that early educational and pharmacological intervention can stop or even reverse its progression. Despite this, diabetes in the majority of patients is poorly controlled, which increases the burden of comorbidity and the cost of disease management. This failure to achieve optimum glycemic control partly results from the limitations of current therapies, which in most cases target the symptoms of the disease but not its underlying causes. Still, a more diligent approach to disease management involving patient education and aggressive intensification of treatment, through combination therapy and timely use of insulin when needed, can control disease. In addition, emerging treatments such as the incretin-based therapies offer the promise of even better glycemic control through mechanisms of action that tackle the disease pathophysiology, not just its symptoms. ■

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Safety and Effectiveness of Modern Insulin Therapy: The Value of Insulin Analogs

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ABSTRACT: Great improvements have been made to insulin preparations over the years, including the development of insulin analogs, which were designed to overcome the disadvantages of traditional human insulins in the treatment of type 1 and type 2 diabetes. Insulin analogs more closely mimic the physiological insulin profile and are therefore associated with an improved balance between glycemic control and tolerability. They are also associated with a lower risk of hypoglycemia, less weight gain, and greater treatment flexibility than human insulins. These benefits, in combination with new insulin delivery devices, such as pens, have greatly improved patients' treatment satisfaction and medication adherence, leading to improvements in clinical outcome. This article reviews the advantages of insulin analogs over human insulin for the treatment of type 1 and type 2 diabetes.

Insulin was first used to treat diabetes in the 1920s. Early advances in therapy consisted of improvements in the purification and modification of pharmaceutical formulations in order to extend their duration of action. The addition of protamine reduced the solubility of insulin at physiological pH, slowing down its absorption after subcutaneous injection and thereby prolonging its action.[1] In 1935, Scott and Fisher[2] further demonstrated that the addition of zinc to insulin prolonged its action profile. Neutral protamine hagedorn (NPH), developed in the 1940s, was the first intermediate-acting insulin containing equal amounts of insulin, zinc, and protamine.[3]

In the early 1980s, recombinant DNA technology enabled the synthesis of human insulin.[4] However, the suboptimal pharmacokinetic and pharmacodynamic characteristics of human insulin, particularly its natural tendency to form absorption-delaying hexamers, prompted further improvements in the insulin molecule. Recent advances in molecular biology have enabled us to modify the insulin molecule, resulting in analogs with pharmacokinetic and pharmacodynamic properties that more closely resemble those of endogenous insulin in healthy persons. Rapid-acting analogs, such as insulin aspart, insulin lispro, and insulin glulisine, are typically used as mealtime insulin replacement because they mimic the physiological insulin response to food intake (**Figure**).[3,5] These analogs, which provide a faster onset and a shorter duration of action than human insulin,[3,5] are administered immediately before meals and reduce the risk of hypoglycemia in the intervals between meals that is often seen with human insulin.[3,4]

Traditional basal (long-acting) insulins such as NPH have suboptimal pharmacodynamic profiles, making them an inadequate replacement for endogenous insulin. After injection, basal insulins exhibit a peak concentration and action followed by waning[6]; they have been associated with significant within-subject absorption variability.[7]

The drawbacks of traditional basal insulins prompted the development of long-acting insulin analogs

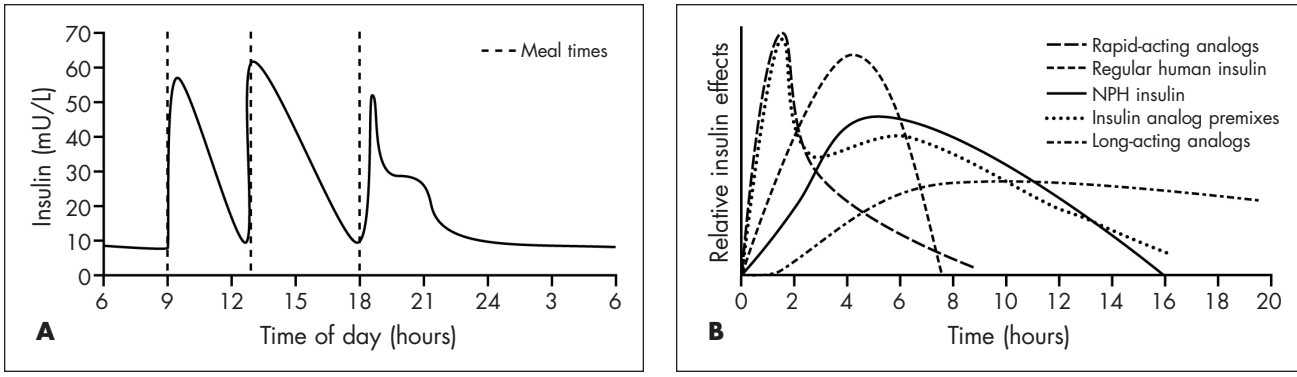

Figure – The physiological plasma insulin profile shows postprandial insulin peaks and basal insulin levels (A). Reproduced with permission from Polonsky KS et al, 1988, *J Clin Invest*, 81, 442-448. © The Biochemical Society (http://www.biochemj.org). The action profile of rapid- and long-acting insulin analogs and insulin analog premixes is seen here (B). Figure courtesy of the Diabetes Teaching Center, University of California, San Francisco. (NPH, neutral protamine hagedorn.)

such as insulin glargine and insulin detemir, which more closely approximate the natural, constant physiological release of insulin (see **Figure**).[3,5] Insulin glargine is injected as a solution, but precipitates upon injection into subcutaneous tissue, delaying absorption.[8,9] Insulin detemir, on the other hand, forms hexamers and reversibly binds to albumin, prolonging its absorption and bioavailability.[10]

The need for convenient, effective, and simultaneous supplementation of both prandial and basal insulin with a limited number of injections prompted the development of premixed insulin analogs,[3,5] which are a mixed suspension of a rapid-acting analog along with its protamine-crystallized form. Several premixed insulin analogs are currently available, including biphasic insulin aspart (BIAsp 70/30; 30% rapid-acting insulin aspart and 70% protaminated insulin aspart) and biphasic insulin lispro (lispro mix 75/25; 25% rapid-acting lispro and 75% protaminated insulin lispro).

CLINICAL TRIAL DATA

A number of clinical trials have shown that insulin analogs have advantages over human insulin in the treatment of both type 1 and type 2 diabetes.

Type 1 diabetes. Patients with type 1 diabetes lack endogenous insulin and therefore rely entirely on injected insulin. Results from large-scale prospective studies such as the Diabetes Control and Complications Trial show that an intensive treatment regimen consisting of a rapid-acting plus a long-acting insulin can help patients with type 1 diabetes achieve better glycemic control, with a lower risk of complications, than less intensive therapy.[11]

Rapid-acting insulin analogs have also been associated with greater reductions in hemoglobin A_{1c} (HbA_{1c}) compared with human insulin. In a randomized, open-label, 6-month trial of 1070 patients with type 1 diabetes, Home and colleagues[12] reported that HbA_{1c} levels were significantly reduced with insulin aspart compared with human insulin (treatment difference, 0.12%; $P < .02$). However, the rapid-acting analog combined with basal human insulin in this study did not reduce HbA_{1c} levels as much as expected. This may have resulted from underuse because of patients' fear of hypoglycemia and investigators' insufficient experience in insulin aspart dosing. Use of shorter-acting prandial insulin necessitated higher doses of basal insulin, exposing patients to high variability in absorption and the potential for nocturnal hypoglycemia. This risk may undermine rapid-acting analogs' advantage of greater reductions in HbA_{1c} levels and could lead to inadequate glycemic control.

Both insulin aspart and insulin lispro have also demonstrated greater postprandial glucose (PPG) control than regular human insulin.[12,13] Insulin aspart plus NPH insulin results in significantly lower PPG levels than human insulin plus NPH insulin (**Table 1**).[12] Similar PPG levels were observed when insulin aspart and human insulin were compared in a randomized, open-label, 6-month study with a 6-month extension period in patients with type 1 diabetes (see **Table 1**).[14] Importantly, improved PPG control has been associated with a reduced risk of long-term cardiovascular complications.[15]

The high risk of hypoglycemia associated with insulin therapy is one of the major concerns in type 1 diabetes.[16] The development of insulin analogs has reduced this risk in patients with type 1 diabetes compared with human insulins.[3] Home and associates[12] reported significantly fewer major nocturnal hypoglycemic events for insulin aspart than for human insulin (8% and 11% of patients, respectively, experienced major hypoglycemia; $P < .05$).

Better overall glycemic control has been achieved with long-acting insulin analogs than with NPH insulin.[5] Many trials have shown that

basal insulin analogs improve the balance between glycemic control and tolerability when compared with NPH insulin[17]; in short, at equivalent glycemic control, the incidence of nocturnal hypoglycemia is typically reduced by 30% from baseline to end of trial for insulin analogs when compared with NPH insulin.[17]

The potential advantages of insulin analogs are best evaluated by comparing all-analog regimens to all-human insulin regimens, because the advantages of each component of the analog regimen are optimized when used in tandem. Greater improvement in glycemic control has been achieved with basal-bolus therapy using insulin analogs compared with an all-human insulin regimen.[18,19] Glycemic control was also shown to improve significantly more with insulin detemir/insulin aspart versus NPH/human insulin in an 18-week, randomized, open-label study of 595 patients with type 1 diabetes (HbA_{1c}, 7.88% vs 8.11%; $P < .001$).[18]

Insulin detemir/insulin aspart improved glycemic control without concomitant weight gain compared with NPH/human insulin.[18] Body weight was 1 kg lower at study end with insulin detemir/insulin aspart than with NPH/human insulin ($P < .001$). The combination of insulin detemir plus insulin aspart also resulted in a lower risk of overall and nocturnal hypoglycemia than NPH/human insulin (21% [$P = .036$] and 55% [$P < .001$], respectively).[18]

In a 32-week, 2-way crossover study of 56 patients with type 1 diabetes, significantly lower HbA_{1c} levels were demonstrated with insulin glargine/insulin lispro than with NPH/human insulin (7.5% vs 8.0%; $P < .001$).[19] Insulin glargine/insulin lispro also reduced the rate of nocturnal hypoglycemia by 44% compared with NPH/human insulin ($P < .001$).[19]

Type 2 diabetes. Many patients with type 2 diabetes could benefit greatly from insulin therapy. However, physicians and patients alike are often reluctant to initiate insulin therapy, so that insulin regimens may not be started until after oral antidiabetic drugs (OADs) have failed. Delaying insulin initiation has been linked to patients' lack of awareness of disease progression, aversion to injection, and patients' and physicians' concerns about hypoglycemia and weight gain.[20,21] Yet several clinical trials have demonstrated a lower risk of hypoglycemia and less weight gain for insulin analogs compared with traditional insulins.[17]

To initiate insulin treatment, long-acting analogs can be used in a simple regimen (generally once daily) in addition to oral therapy. In studies of insulin-naive patients with type 2 diabetes, use of basal analogs has been associated with significant improvements in glycemic control and with a lower risk of hypoglycemia compared with NPH insulin.[17]

Aggressive titration of basal analogs has generally resulted in mean HbA_{1c} level decreases of about 1.5%,[17] meaning that guideline-recommended HbA_{1c} targets (< 7.0%) are achievable if HbA_{1c} is not already in excess of 8.5%. For example, in a 26-week, randomized, parallel, treat-to-target trial of 476 insulin-naive patients with type 2 diabetes who were inadequately controlled with OADs, the majority of patients (70%) achieved HbA_{1c} target levels of 7.0% or less with insulin detemir and NPH insulin. However, a significantly greater proportion of patients in the detemir group achieved these targets without hypoglycemia during the last 12 weeks of treatment (26% vs 16%; $P < .01$).[22] Patients receiving insulin detemir also achieved HbA_{1c} targets with significantly less weight gain than those receiving NPH insulin (1.2 kg vs 2.8 kg, respectively; $P < .001$).[22]

Similar results were observed in a treat-to-target trial of 756 overweight patients with type 2 diabetes inadequately controlled with OAD therapy.[23] With the addition of once-daily insulin glargine or NPH insulin to existing OAD therapy, about 60% of patients achieved HbA_{1c} target levels of 7.0% or less, and significantly more patients in the glargine group versus the NPH insulin group attained these targets without nocturnal hypoglycemia (33% vs 27%, respectively; $P < .05$).[23]

Three different insulin analog regimens were compared in the **T**reat-to-**T**arget in **T**ype **T**wo (4-T) study, which included 708 patients with type 2 diabetes inadequately controlled with OADs.[24] Patients were randomized to receive twice-daily biphasic insulin aspart, 3-times daily

Table 1 – Comparison of postprandial glucose levels after main meals following administration of insulin aspart plus NPH or human insulin plus NPH

	Postprandial glucose (mg/dL)					
	After breakfast		After lunch		After dinner	
	Insulin aspart	Human insulin	Insulin aspart	Human insulin	Insulin aspart	Human insulin
Home[12]	160[a]	182	144[b]	153	151[b]	162
Raskin[14]	156[c]	185	137[c]	162	153[c]	168

NPH, neutral protamine hagedorn.

[a] $P < .001$, [b] $P < .01$, [c] $P < .05$.

Table 2 – Treatment effects of insulin analogs in a basal-bolus regimen

	HbA_{1c} change (%)	FPG within-subject variability (mg/dL)	Weight change (kg)
Haak[27]			
Insulin detemir/insulin aspart	− 0.2	23.4[a]	1.0[a]
NPH insulin/insulin aspart	− 0.4	25.2	1.8
Raslová[28]			
Insulin detemir/insulin aspart	− 0.65	21.6[b]	0.51[a]
NPH insulin/insulin aspart	− 0.58	27.7	1.13

HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose.
Significant treatment difference: [a] $P < .05$, [b] $P < .001$.

prandial insulin aspart, or once-daily basal insulin detemir. At 1 year (the first phase of the 3-year trial), the 3 analog regimens were associated with clinically relevant and sustainable reductions in HbA_{1c}. Premixed and rapid-acting analog regimens lowered HbA_{1c} to a similar extent (−1.3% and −1.4%, respectively), but significantly more than the basal insulin regimen (−0.8%; $P < .001$ for both comparisons). However, patients treated with the premixed and rapid-acting insulin analog regimens had a greater risk of hypoglycemia (5.7 and 12.0 events/patient-year, respectively, vs 2.3 events/patient-year; $P = .04$) and weight gain (4.7 kg and 5.7 kg, respectively, vs 1.9 kg; $P < .001$) than those who received the basal regimen.[24] Basal insulin therefore appears to be the most tolerable insulin initiation regimen, though intensification may be necessary over time.

As the disease progresses, patients with type 2 diabetes will eventually need to supplement both basal and prandial insulin. Premixed insulins can be prescribed once or twice daily for insulin intensification when a basal insulin regimen has become inadequate. As Garber and colleagues[25] noted, premixed insulin analogs have several advantages over premixed human insulins. Although both have demonstrated similar HbA_{1c} control (with ~60% to 70% of patients achieving $HbA_{1c} < 7.0\%$) and similar rates of minor hypoglycemia (~60% of patients), a lower risk of major hypoglycemia was seen for premixed analogs compared with premixed human insulin (0% to 5% vs 10% to 15% of patients, respectively).

Lower PPG levels have also been observed for premixed insulin analogs versus premixed human insulins. For example, postprandial control was significantly greater for BIAsp 70/30 when compared with biphasic human insulin 30 (BHI 30) and lispro mix 75/25 (17% [$P < .001$] and 10% [$P < .05$] lower postprandial blood glucose values, respectively) in a randomized, open-label, single-dose, 3-way crossover trial of 61 patients with type 2 diabetes.[26]

Advanced type 2 diabetes will eventually require basal-bolus treatment. Basal analogs in basal-bolus therapy have resulted in less weight gain and less within-person variation in blood glucose than NPH insulin.[27,28] A comparison of 2 basal-bolus regimens (insulin detemir plus insulin aspart or NPH insulin plus insulin aspart) demonstrated significant and comparable reductions in HbA_{1c} levels from baseline in a 26-week, randomized, open-label trial of 505 patients with type 2 diabetes (**Table 2**).[27] However, within-subject variability of fasting blood glucose and weight gain was significantly lower with insulin detemir than with NPH insulin.

An all-analog regimen (insulin detemir plus insulin aspart) showed similar glycemic control when compared with an all-human insulin regimen (NPH insulin plus regular human insulin) in 395 patients with type 2 diabetes treated for 22 weeks in an open-label, randomized trial,[28] but insulin detemir/insulin aspart treatment resulted in significantly lower within-person daily glucose variation and significantly less weight gain (see **Table 2**).

The effect of transferring patients with type 2 diabetes on prandial rapid-acting analogs (insulin aspart/lispro) in combination with bedtime NPH insulin to morning insulin glargine plus insulin aspart/lispro was also compared with the effect of continuation of the previous NPH treatment plus insulin aspart/lispro in a 6-month randomized trial. This trial demonstrated that bedtime insulin glargine improved glycemic control (HbA_{1c}, −0.6% vs −0.1%; $P < .01$) without an increase in hypogly-

cemia (0.78 to 0.79 episodes/patient-month) compared with NPH insulin treatment.[29]

OBSERVATIONAL TRIAL DATA

Large observational studies can play an important role in investigating treatment outcomes in large, heterogeneous populations, because they provide real-life data that complement the results from randomized controlled trials. Many large observational studies have investigated the safety and effectiveness of insulin analogs.

Type 1 diabetes. Insulin analogs have been proven to have good tolerability and improve glycemic control without an increase in hypoglycemia in patients with type 1 diabetes in routine clinical practice.[30,31] The PREDICTIVE study is a large, multinational observational study that investigated the safety and efficacy of insulin detemir in clinical practice.[30,31] The PREDICTIVE European cohort (N = 20,531) included 7420 patients with type 1 diabetes. Of these patients, a subgroup of 4782 switched either from a basal-bolus regimen with NPH insulin or insulin glargine to insulin detemir basal-bolus therapy, or from a human insulin basal-bolus regimen to insulin detemir/insulin aspart regimen.[30] Significant improvements in glycemic control were seen for all patients ($P < .0001$), with HbA_{1c} levels decreasing by 0.5%, 0.4%, and 0.6% in patients previously receiving NPH insulin, insulin glargine, and human basal-bolus insulins, respectively. Glycemic control was attained with a significant reduction in major hypoglycemia (55%, 51%, and 54%, respectively; $P < .0001$) and no weight gain.

Type 2 diabetes. Several observational studies have also investigated the safety and effectiveness of insulin analogs in routine clinical practice for the treatment of type 2 diabetes. The PREDICTIVE European cohort (N = 20,531) included 12,981 patients with type 2 diabetes,[32] of which a subgroup of 293 patients transferred from a regimen of OAD therapy plus 1 or 2 basal injections of NPH insulin or insulin glargine to a regimen of OAD therapy plus insulin detemir, significantly improving glycemic control (**Table 3**). A lower incidence of hypoglycemia was also seen, with a significant decrease in body weight.[32]

The long-term effectiveness and safety of insulin glargine was further investigated in a large observational study of 12,216 patients with type 2 diabetes inadequately controlled by OAD therapy,[33] in which the addition of insulin glargine to OAD therapy resulted in improved glycemic control (HbA_{1c}, −1.7%; fasting plasma glucose [FPG], −70.2 mg/dL). This improvement was achieved without an increase in body weight and with a relatively small risk of hypoglycemia (0.1% of patients).[33]

Premixed insulin analogs are also routinely prescribed for the treatment of type 2 diabetes. In PRESENT, a large, multinational observational study of 22,857 patients with type 2 diabetes previously uncontrolled on human insulin with or without OADs or OAD therapy, BIAsp 70/30 was shown to be safe and effective for the treatment of type 2 diabetes.[34] BIAsp 70/30 therapy resulted in significantly improved glycemic control for all patients. However, improvements were greater for insulin-naive patients than for those previously treated with insulin (HbA_{1c} reduced by ~2.2% and ~1.6%, respectively; $P < .05$ for both). FPG and PPG levels were significantly reduced in both insulin-naive patients (~81 mg/dL and ~122.4 mg/dL, respectively; $P < .05$ for both) and in those previously treated with insulin (~52.2 mg/dL and ~90 mg/dL, respectively; $P < .05$ for both). Target HbA_{1c} levels were attained by ~25% of patients, but insulin-naive patients achieved these targets at a lower dose of BIAsp 70/30. Frequency of hypoglycemic events was also higher for patients previously treated with insulin than for insulin-naive patients (~2.35 vs ~2.18 episodes/patient-year).[34]

INSULIN DELIVERY DEVICES

Traditional insulin "vial and syringe" delivery has several disadvantages, including the potential for dosing inaccuracies—particularly among children or elderly patients who may have difficulty handling a vial and syringe or selecting the appropriate dose. Injection anxiety and social embarrassment may also have a negative impact on patient adherence.[35,36] These disadvantages are now being overcome by advances in insulin delivery devices.

The introduction of insulin pens in the 1980s greatly increased the flexibility and convenience of insulin administration.[37] They are also associated with less painful injections and less social embarrassment, thereby increasing patients' quality of life.[38]

In a randomized crossover trial that assessed insulin-treated patient preference for a prefilled disposable pen device (FlexPen® [Novo Nordisk A/S]) versus vial and syringe, 85% of patients thought the pen was more discreet for public use.[39] Furthermore, usability and patient preference were compared for 4 prefilled, disposable, insulin pens (Solostar® [sanofi aventis], Humulin®/Humalog® [Eli Lilly and Company], FlexPen, and a prototype pen [sanofi aventis]).[40] Both the Solostar pen and FlexPen were found to have high patient usability, with 94% and 90% of patients, respectively, successfully completing the usability assessment test (patients prepared each pen for injection into a receptacle). A higher proportion ($P < .05$) of patients expressed an overall preference for the Solostar pen (53%) compared with FlexPen (31%) and Humulin/Humalog (15%), as determined during a

question-and-answer session. Patients found the Solostar pen easier to use properly, and they appeared to prefer the tactile feel of the Solostar pen compared with the FlexPen and Humulin/Humalog pen.[40]

However, recently the injection force of the Next Generation FlexPen® (NGFP), a modified version of FlexPen, was compared with that of Solostar.[41] This study compared the injection force of 24 pens of each type during the delivery of 60 IU of insulin at 3 constant push-button speeds. It was observed that NGFP had an 18% to 45% lower injection force compared with Solostar.[41]

Prefilled insulin pens, in particular, are associated with improved treatment adherence versus the vial and syringe,[35] resulting in improved glycemic control, lower incidence of hypoglycemic events, and better long-term clinical outcomes.[35] A study of 1156 patients with type 2 diabetes previously treated with human insulin or an insulin analog administered with a vial and syringe evaluated the effect on adherence of transferring to a prefilled analog pen device.[35] Switching from the vial and syringe to a pen was shown to significantly improve treatment adherence (as measured by a medication possession ratio ≥ 80%) from 62% to 69% ($P < .01$). The likelihood of experiencing hypoglycemic events also fell by 50% when a prefilled insulin pen was used ($P < .05$).

Pen devices also utilize small-gauge needles, making them much more comfortable to use than traditional syringes.[42] In a comparison of 2 types of needle design and diameter (NovoFine® 32G 6-mm [Novo Nordisk A/S] and Micro Fine Plus® 31G 5-mm [Nippon Becton Dickinson Co Ltd]) in patients with diabetes, both factors played an important role in reducing injection pain.[43] On a questionnaire used by Iwanaga and Kamoi[43] with a scale ranging from −100 to +100, in which a higher score indicated a better outcome, use of a tapered needle (NovoFine) was associated with less painful insertions, less bruising, and less bleeding than the standard needle (Micro Fine Plus). The tapered needle was also rated as more convenient and easy to use.[43]

CONCLUSIONS

Insulin analogs have greatly improved type 1 and type 2 diabetes

Table 3 – Observed changes after 14 weeks of insulin detemir therapy: results of the PREDICTIVE study[31]

		NPH group	Glargine group
HbA_{1c} (%)	Baseline	8.1 ± 1.4	8.1 ± 1.2
	Mean change from baseline	– 0.2 ± 1.2[a]	– 0.6 ± 0.9[b]
FPG (mg/dL)	Baseline	153 ± 39.6	162 ± 45
	Mean change from baseline	– 18.0 ± 39.6[b]	– 25.2 ± 43.2[b]
Fasting glucose variability (mg/dL)	Baseline	23.4 ± 21.6	21.6 ± 18.0
	Mean change from baseline	– 7.2 ± 19.8[b]	– 5.4 ± 18.0[b]
Overall hypoglycemia (episodes/patient-year)	Baseline	11.7	4.3
	Mean change from baseline	– 8.7[b]	– 3.5[c]
Nocturnal hypoglycemia (episodes/patient-year)	Mean change from baseline	– 5.5[b]	– 1.2[a]
Body weight (kg)	Mean change from baseline	– 0.7[c]	– 0.5[a]

NPH, neutral protamine hagedorn; HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose.
Data are mean (SD) vs baseline: [a] $P < .05$, [b] $P < .0001$, [c] $P < .01$.

treatment by mimicking the physiological insulin profile more closely than traditional insulins. While rapid-acting insulin analogs were developed to replace prandial insulin and to mimic the physiological response to ingestion of food, long-acting analogs supplement or replace basal insulin to mimic the constant physiological release of insulin seen in healthy persons between meals. Premixed insulin analogs were later developed to supplement both prandial and basal insulin needs in a more convenient and effective way. Numerous clinical trials and observational studies have demonstrated the advantages of insulin analogs over human insulin regimens, and insulin analogs are associated with an improved balance between glycemic control and tolerability compared with human insulin. The advances in insulin preparations have also encouraged the improvement of insulin delivery devices such as pens, which leads to improved treatment satisfaction and medication adherence, resulting in better clinical outcomes. ■

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Addressing Barriers to Timely Intensification of Diabetes Care: The Relationship Between Clinical Inertia and Patient Behavior

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ABSTRACT: Evidence has shown that effective blood glucose control can reduce long-term diabetes complications, and a plethora of clinical guidelines have recommended glycemic targets. Yet many patients with diabetes have poor glycemic control, which may be caused by a number of factors including clinical inertia: the failure to initiate or augment therapy when it is clinically indicated. This article will examine how health care providers and patients can work together to address the issue of clinical inertia and improve patients' willingness to accept appropriate treatment changes.

Effective control of blood glucose levels reduces the development of long-term microvascular complications[1-3] and may reduce longer-term cardiovascular disease.[2-7] In order to optimize long-term prognosis, diabetes care should be intensified as soon as a patient's current therapeutic regimen can no longer maintain glucose levels within the recommended targets. However, many real-world patients do not achieve such targets.

National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2004 show that 44% of patients with type 2 diabetes did not have hemoglobin A_{1c} (HbA_{1c}) levels within the American Diabetes Association (ADA) target range, which is lower than 7%.[8,9] Rigorous glycemic control targets may not be appropriate for all elderly patients or those with certain comorbidities. Yet for most persons with diabetes, maintaining glycemic control within the recommended ranges should be the treatment goal.

Given the range of diabetes care interventions available and the clear clinical guidelines on their appropriate use, why are so many patients not achieving glycemic targets? Clinical inertia on the part of health care providers (HCPs) is one reason. The term "clinical inertia" has been used by Phillips and associates[10] to describe the failure of HCPs to initiate or intensify therapy when indicated (ie, recognition of a problem but failure to act). The term is usually used in association with diabetes, hypertension, hyperlipidemia, and other chronic diseases in which HCPs and patients try to maintain clinical parameters within defined targets in order to avoid long-term adverse complications.[11]

Since failure to achieve short-term clinical targets does not necessarily result in adverse symptoms, the HCP may continue an ineffective therapy for a longer period than is appropriate.[11] In this form of clinical inertia, called clinical myopia, HCPs or patients may prioritize short-term rewards (eg, avoidance of having to make potentially difficult clinical choices/lifestyle changes) over long-term benefits (avoidance of complications).[11]

The HCP may cite many other reasons for clinical inertia including concerns that patients will be unwilling or unable to manage intensification of care, the medical office does not have the time or resources to adequately implement treatment intensification, or intensification is likely to

be thwarted by lack of adherence on the part of the patient.[10] Simple organizational factors, such as the inability to easily access the patient's most recent HbA_{1c} results or not having implemented clear, written guidelines defining diabetes care standards for their center, may also delay the HCP's decision to intensify diabetes care.

Failure to achieve glycemic targets may also reflect patients' difficulties in effectively self-managing their disease. For the majority of patients with type 2 diabetes, lifestyle changes that support and encourage weight loss and increased activity form the basis for treatment. Despite the benefits of this form of therapy, many patients find it difficult to maintain such changes over time. Current ADA guidelines recommend initiation of metformin along with lifestyle changes at the time of diagnosis as an added measure to help patients achieve their targets.[9]

Patients display clinical inertia by resisting treatment intensification. Feelings of guilt over poor adherence to lifestyle changes create a rationale for giving the current regimen yet another chance.[12] This attitude may reflect the fact that many patients do not fully understand the progressive and serious nature of diabetes and the resulting need for treatment intensification.[13]

Depression and other mental health disorders can also impair patients' ability to manage their diabetes. The Diabetes Attitudes Wishes and Needs (DAWN) study found that 41% of persons with diabetes had poor psychological well-being, which their HCPs felt could adversely affect their ability to manage their disease.[14] Although psychological difficulties are common, only 12% of patients reported that they had received psychological support in the previous 5 years,[14] suggesting a deficiency in providing psychosocial care for individuals with diabetes.

The aim of this article is to highlight the reasons behind delayed treatment intensification, focusing on patient and HCP factors that contribute to the delay and examining the ways in which patients and HCPs can be supported to improve outcomes.

PATIENT NEEDS AT DIAGNOSIS AND BEYOND

Patients with type 2 diabetes should be offered a variety of support measures at the time of diagnosis to help them understand their disease and to manage expectations about their current and future treatment needs. It is important that educational initiatives stress the importance of diet, exercise, and weight management; provide an overview of the available pharmacological interventions; and encourage and empower patients to actively self-manage their diabetes.[9,15,16] Patients need reassurance that they can indeed manage their diabetes, but it is important for HCPs to stress the progressive nature of the disease, setting the expectation that the treatment will need to be changed over time. Even when patients are taking every step to manage the disease effectively, changes in therapy will still be necessary.[17]

A range of treatment options are available for persons with type 2 diabetes. These include lifestyle interventions that encourage positive changes in diet and activity levels as well as oral antidiabetic drugs (OADs) such as metformin, sulfonylureas, and thiazolidinediones. There are also therapies that target the incretin system, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1)–receptor agonists in addition to a variety of insulins. Insulin analogs have been engineered to have pharmacokinetic properties that more closely resemble physiological insulin, mimicking basal and prandial insulin patterns.

While there is an important need to educate patients about their disease, diabetes self-management education (DSME) should also facilitate positive behavioral changes. The American Association of Diabetes Educators (AADE) has identified 7 self-care behaviors (healthy eating, being active, blood glucose monitoring, taking medication, problem solving, healthy coping, and reducing risks)[18] that DSME should aim to facilitate through education and by identifying and addressing barriers to behavior changes.[17] DSME should be individualized, taking account of factors including medical history, age, attitudes to health, cultural factors, disease knowledge, current ability to self-manage, and level of social and financial support.[17] A team approach, including the primary care physician, other specialists (such as an endocrinologist, nurse practitioner, ophthalmologist, podiatrist, or dietician), and a diabetes educator, is recommended to provide the most comprehensive support for patients.[19]

CLINICAL INERTIA AND DIABETES OUTCOMES

Because poor glycemic control is both an indicator that treatment should be changed and a predictor of poor outcomes,[20] it is difficult to measure the effects of clinical inertia unless HCPs control for confounding factors. Treatment intensification is likely to be associated with worse glycemic control because it identifies a population of patients with more severe disease, while patients not receiving treatment intensification may have better outcomes purely because their diabetes is less severe.

A different approach has been taken by Berlowitz and colleagues,[20] who examined a cohort of persons with diabetes receiving care at Veterans Affairs medical centers. This retrospective study compared the number of actual observed intensifications

in patients' diabetes care over a period of about 16 months with the number of predicted treatment intensifications, based on clinical status at each visit. Patients had a mean of 8.8 clinic visits per year. Active treatment intensification occurred when the number of actual treatment intensifications matched or exceeded the predicted number, while clinical inertia occurred when there were fewer actual treatment intensifications than predicted.

The results of this study identified widespread clinical inertia. Despite the fact that many persons had poor glycemic control, treatment was intensified in approximately 1 in 10 visits, and in only 32% of individuals whose most recent HbA_{1c} was higher than 8%.[20] The study also demonstrated that patients whose diabetes care was most actively intensified had better HbA_{1c} outcomes. For example, poor glucose control (classified as HbA_{1c} > 8%) was observed in over half of the persons in the lowest 20% for treatment intensity (eg, those whose therapy had been intensified the least) compared with 36% of the remaining patients (whose diabetes had been managed more actively).

The UK Prospective Diabetes Study (UKPDS) demonstrated that improving glycemic control through more intensive diabetes care resulted in long-term risk reductions for such type 2 diabetes complications as microvascular disease, myocardial infarction, and death from any cause.[21] By failing to adjust diabetes care appropriately, therefore, clinical inertia leads to inadequate glycemic control, and the patient's risk of developing diabetic complications increases.

Table 1 – Negative beliefs about insulin

Negative belief about insulin	Frequency in all patients (%)	Frequency in patients unwilling to take insulin (%)
Permanence: once I start insulin I can never quit	45	53
Restrictiveness: my daily life would be harder	45	56
Low self-efficacy: I'm not confident I can handle the demands of insulin therapy	44	58
Personal failure: insulin therapy would mean I've failed	43	55
Hypoglycemia: insulin may cause serious problems with my blood sugar	41	49
Illness severity: taking insulin means my diabetes will become a more serious disease	38	47
Pain: I couldn't take a needle every day; it would be too painful	34	51
Expected harm: insulin therapy can cause problems such as blindness	17	10

CLINICAL INERTIA AND PATIENT RESISTANCE WITH RESPECT TO INSULIN INITIATION

If lifestyle interventions and metformin do not help patients achieve their glycemic goals, HCPs should consider adding a second medication, such as a sulfonylurea or a basal insulin.[9] The addition of a GLP-1 receptor agonist may also offer benefits in this setting because these agents are associated with weight loss and a low risk of hypoglycemia.[9] While insulin is more effective at lowering hyperglycemia and is an appropriate treatment choice for patients with HbA_{1c} levels higher than 8.5%,[9] resistance to insulin initiation is prevalent among both patients and their HCPs.[12]

Polonsky and colleagues[22] coined the term "psychological insulin resistance," describing patients who are reluctant about or refuse insulin therapy because of their misconceptions about this medication. In one study, 1267 individuals with type 2 diabetes completed an anonymous questionnaire about insulin. Of the 708 who were not taking insulin, 28% described themselves as unwilling to take insulin if prescribed, 24% were slightly willing, 23% were moderately willing, and 24% were very willing.[22] Psychological insulin resistance was more common in women (32% unwilling) and ethnic minorities (35% unwilling). Persons who had a mean of 3 or more negative beliefs about insulin had a higher magnitude of psychological insulin resistance.[22]

The frequency of negative beliefs among all patients compared with those with psychological insulin resistance is shown in **Table 1**. Not

surprisingly, the frequency of these fears was higher in patients who were unwilling to take insulin. Other patient concerns include a fear of becoming addicted to insulin[13] and the belief that long-term insulin use may cause complications.[17] In addition, patients may have concerns about weight gain, hypoglycemia, lifestyle restrictions, painful injections, and loss of control/feelings of failure over their disease.[13,23,24] Feelings of social stigma relating to injecting in public are also common[25,26] and may result in avoidance of social engagements or skipping insulin doses when patients are out in public.

HCP RESISTANCE TO INSULIN THERAPY

HCPs contribute to delays in insulin initiation. A questionnaire survey of 505 US primary care physicians reported that 80% thought their patients were afraid of insulin therapy, 72% felt that their patients would be reluctant to accept a prescription for insulin, and 66% viewed insulin initiation as one of the most difficult aspects of managing diabetes.[27]

These attitudes prevailed despite the fact that approximately 80% of physicians thought their patients felt physically much better once they became accustomed to insulin treatment and felt that the benefits of insulin outweighed the potential risks of hypoglycemia and weight gain.[27] The study also identified misconceptions about insulin among some HCPs. Forty percent felt that patients would not require insulin initiation if they followed their physician's treatment recommendations, and 33% felt that raising plasma insulin levels would increase cardiovascular risk.

In another study of 157 family physicians, reasons for not initiating insulin included patient noncompliance with treatment (92%), fear of hypoglycemia in a specific patient (80%), the feeling that patients would not be able to cope with the pain of regular blood tests (54%) or insulin injections (48%), and patient age.[13] The DAWN study further identified a widespread attitude among 50% to 55% of US HCPs that insulin initiation should be delayed until absolutely necessary.[12] Delay in prescribing OADs was also strongly associated with delay in prescribing insulin.[12] The recent publication of clinical guidelines[9,15] suggests that the need to address HCP attitudes about insulin and its initiation still exists. Any efforts to address clinical inertia among HCPs will need to target all classes of diabetic medications.

OVERCOMING BARRIERS TO TREATMENT

The ways in which diabetes care is organized within a practice can reduce clinical inertia. For example, computerized systems or flow sheets (simple forms that can be included with a patient's notes that prompt HCPs to consider treatment intensification) can assist in clinical decision making. To ensure that recommended tests and disease interventions are carried out at appropriate intervals, diabetes flow forms may include current treatment targets and checklists. For example, small but significant improvements in adherence to diabetes assessment (55% vs 50%; $P = .02$) and treatment guidelines (80% vs 75%; $P = .004$) were observed in practices that used diabetes flow sheets, compared with those that had no such systems.[28]

At a primary care clinic, performance feedback in the form of short, biweekly, face-to-face meetings of medical residents with an endocrinologist to review individual cases was shown to be effective in improving treatment intensification behavior.[29] Feedback or feedback plus reminders (flow sheet and treatment recommendations) significantly increased the tendency to intensify therapy ($P < .01$ feedback vs other groups), with improvement maintained over 3 years. These studies show that simple interventions in practice organization and systems that prompt HCPs to consider treatment intensification can reduce clinical inertia.

There is broad agreement among HCPs that increased involvement of diabetes educators will improve diabetes care.[30] These health care professionals often have more time to spend with patients, are better listeners, and may provide better patient education than physicians.[30] Practices that embrace diabetes educators, nurse case managers, and diabetes self-management programs have demonstrated positive quality of care and patient outcomes.[31-33]

It is likely that patients who have a better understanding of their disease will be more empowered to take an active role in disease management, demonstrate better day-to-day diabetes care, and be more open to treatment intensification as their disease progresses. A review of 3 meta-analyses, 7 primary studies, and 7 systematic reviews examining the effects of DSME demonstrated that it was effective in improving measures such as glycemic control, psychosocial well-being, and quality of life.[34] Improvements in glycemic control are typically observed during the first 1 to 6 months following DSME, after which benefits tend to be reduced.[34] This finding suggests that DSME needs to be an ongoing process rather than a one-time intervention. Although clinical guidelines recommend that DSME be an integral part of any diabetes care program, one study reported that approximately 60% to 70% of patients have not received any formal DSME.[18] To address this deficiency, the health care system must widen access to ensure that patients receive the training they need to effectively self-manage their diabetes.

Table 2 – Strategy for success in insulin initiation

1. As a health care provider, recognize your attitudes to insulin and do not allow them to influence the way you present insulin initiation to your patient.
2. Discuss the potential need for insulin initiation early in the disease process.
3. Identify and discuss patient attitudes to insulin.
4. Find out whether the patient has family members or friends who have received insulin treatment, and whether they had a positive or negative experience.
5. Explore the patient's major concerns about insulin.
6. Avoid viewing insulin initiation in a moral context (eg, reflecting a failure to adhere to previous care regimens).
7. Be aware of and acknowledge the patient's emotional feelings about diabetes.
8. Develop a plan in cooperation with the patient that will move him or her toward clinical goals.

Adapted from Reid T. *Insulin.* 2007.[24]

Overcoming specific barriers to insulin treatment. In order to successfully initiate insulin, HCPs must help their patients overcome common barriers to intensifying diabetes therapy, while simultaneously addressing the specific concerns their patients may have about insulin. As with any change in treatment, options should be discussed and the HCP and patient should work together to develop a plan that will achieve clinical goals (**Table 2**).[24]

In practical terms, modern insulin analogs help patients make the transition to insulin by reducing the risks of hypoglycemia.[9] Prefilled insulin pens can help patients make the transition to insulin[35] by providing easier, more convenient and discrete dosing than syringe administration,[26,36] and by using needles that reduce injection pain.[37] All of these factors have positive effects on patient preference and treatment satisfaction[25,38,39] and can improve adherence.[35]

Patients also report improved quality of life after insulin initiation. In one study, insulin initiation with a structured diabetes treatment and teaching program was associated with improvements in diabetes-related quality of life ($P = .03$), reduced worries about the future ($P = .02$), reduced daily struggles ($P = .01$), and less fear of hypoglycemia ($P < .001$) 6 months after initiation when compared with pre-insulin treatment.[40] These improvements were also associated with improved metabolic control (HbA_{1c} level was 10.0% ± 1.4% at baseline and 8.4% ± 1.4% at 6 months following insulin initiation).

KEY RECOMMENDATIONS

Increased access to DSME and the participation of diabetes educators can give patients a sense of control and autonomy in the management of their disease. Educational interventions should highlight the fact that type 2 diabetes is a progressive disease, treatment will need to be intensified to address disease progression, and intensification is not a sign of failure on the part of the patient. Barriers to intensifying therapy should be identified and addressed on an individual basis.

Given the competing demands faced by physicians, there is not only a need but also an opportunity for diabetes educators to take on a greater role in diabetes care, and for clinical practices to take greater advantage of this resource. Simple measures such as electronic records, diabetes flow sheets, and regular performance appraisals/feedback can help reduce clinical inertia.

Clinical inertia is a widespread problem in patients with type 2 diabetes that leads to poor glucose control and the associated increased risks of long-term diabetic complications. Negative attitudes and barriers to appropriate treatment intensification affect both patients and their HCPs, so interventions to address clinical inertia should address both of these groups. ■

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Insulin Intensification: A Patient-Centered Approach

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Diabetes mellitus is the most common metabolic abnormality, and the disease is growing at an alarming rate—there are currently an estimated 24 million people living with the condition in the United States.[1] Ninety percent of people with diabetes have type 2 diabetes, which is most often caused by a combination of insulin resistance and β-cell dysfunction.

Type 2 diabetes is now seen at all ages, including childhood and adolescence. As a result, physicians typically begin treating patients with diabetes at a younger age and are involved in their care for many years. It is therefore important to understand the natural history of the disease and how best to treat it with the increasing variety of medications that are available.

This challenge is especially great for primary care physicians, who are increasingly responsible for the care of persons with diabetes. Since the disease disproportionately affects minority groups, physicians also need to understand the many cultural issues that can affect disease management in their patients. While many organizations have published guidelines for diabetes management, the practicing clinician should be able to individualize therapy and understand that guidelines serve as just that—a guide, not a mandate. For example, aggressive titration of insulin for an elderly patient may incur an increased risk of hypoglycemia, while a younger patient may be able to maintain blood glucose levels close to euglycemia. Organizations such as the National Commission on Diabetes have developed strategies for bridging the gap between clinical findings and public health practice, observing that "if ignored . . . real-world situations can render interventions ineffective."[2] Primary care physicians must learn to balance the need to follow current guidelines with a patient-centered approach.

A joint consensus statement published in 2008 by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends that glycosylated hemoglobin (HbA_{1c}) be maintained at levels lower than 7% and as close to normal as possible without increasing the risk of hypoglycemia.[3] While diet and exercise alone may initially be sufficient to help patients reach this target, 75% of patients will require further intervention within 3 years.[4] The ADA and EASD therefore recommend starting metformin at the time of diagnosis in the hope that HbA_{1c} goals will be achieved more effectively than with lifestyle modifications alone.

While concomitant use of oral antidiabetic drugs (OADs) can lower HbA_{1c} concentrations by a further 0.5% to 2.0%, insulin will ultimately have to be added to most therapeutic regimens in order to preserve good glycemic control. Basal insulin is often used to initiate insulin treatment and bring fasting blood

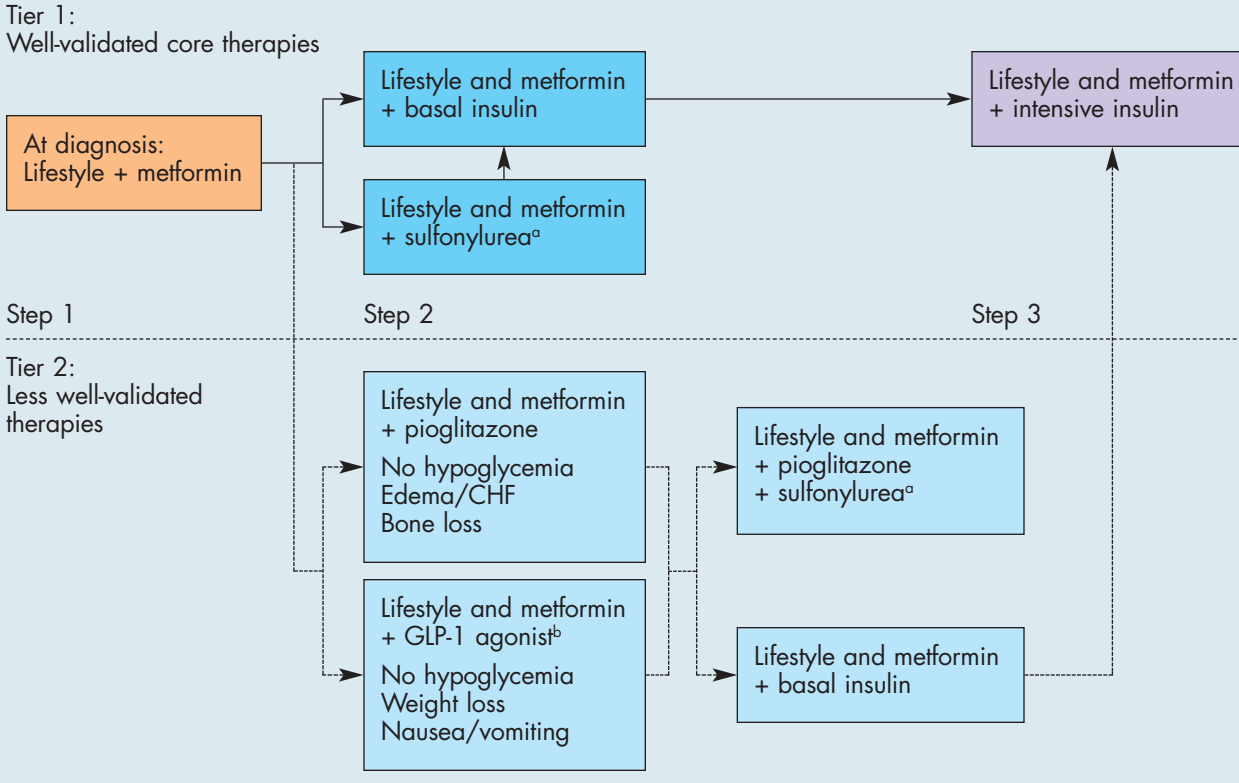
glucose (FBG) toward normal levels. When this happens, OADs are usually continued at their current dose. Premixed insulins, which incorporate both a slow- and a rapid-acting component in a single injection, are also frequently used to initiate insulin treatment. A premixed insulin given at supper lowers both post-supper and FBG levels. However, as β-cell function progressively diminishes, insulin treatment will almost certainly require intensification. In this case, ADA and EASD guidelines suggest use of a stepwise approach that can help the clinician intensify a variety of different starting insulin regimens (**Algorithm**).[3]

INITIATION, OPTIMIZATION, AND INTENSIFICATION OF INSULIN THERAPY

Once insulin treatment has been initiated, each patient's regimen must be optimized. For patients started on basal insulin, for example, the dose may have to be increased to lower FBG to the target range. Unfortunately, the progressive loss of β-cell function means that optimization alone is often insufficient to achieve therapeutic goals, and intensification, using insulins that address both prandial and basal requirements, is needed.

It has been demonstrated that both fasting and postprandial glucose (PPG) concentrations contribute to HbA_{1c} levels, and that at higher levels, FBG contributes more to the HbA_{1c} than PPG concentrations.[5-7] As HbA_{1c} levels approach 7%, however, PPG contributes more than FPG. In patients whose fasting glucose is within goal but whose HbA_{1c} is above 7%, the focus should then be on prandial insulin requirements and on lowering postprandial glucose if necessary. This can be achieved by using premixed insulins 2 or 3 times a day,

ADA and EASD Consensus Algorithm for Metabolic Management of Type 2 Diabetes Mellitus as Need for Intensification Progresses



ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; CHF, congestive heart failure; GLP-1, glucagon-like peptide-1.

[a] Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

[b] Insufficient clinical use to be confident regarding safety.

or by adding prandial insulin at appropriate meals.

The following case histories demonstrate an approach to intensifying insulin using various regimens in patients with type 2 diabetes who have inadequate glycemic control on their current treatment.

Case Study 1: Kimberley

Kimberley, a 48-year-old woman, received a diagnosis of type 2 diabetes 6 years ago. At the time of diagnosis, her HbA_{1c} was 9.0%, and metformin was started concurrently with lifestyle modifications. After 6 months, her HbA_{1c} decreased to 7.6%, then rose to 8.6% a year later. At that time, she was started on a sulfonylurea, then switched to a dipeptidyl peptidase-4 (DPP-4) inhibitor because of weight gain. Kimberley maintained an HbA_{1c} of 7.2% to 7.5% for 1 year on this regimen, but about 6 months ago it rose again, to 8.6%. She was started on twice-daily neutral protamine hagedorn (NPH) insulin, and has gained another 10 lb since then. Her current medications include metformin 1000 mg twice daily, sitagliptin 100 mg daily, and 20 units of NPH insulin in the morning and 10 units at bedtime. Kimberley is concerned about the weight gain she has experienced and does not like to take insulin twice daily (she sometimes forgets her morning dose), so she would like to consider an alternative insulin regimen. She is currently 92 kg, with body mass index (BMI) of 38.2 kg/m², HbA_{1c} of 8.4%, and FBG of 180 mg/dL.

Recommendation. Kimberley's FBG is elevated, which is not surprising given that she is taking only 10 units of NPH insulin at bedtime. Kimberley's total daily dose of insulin is 30 units. She is also reluctant to take insulin twice daily and is concerned that this particular insulin has been associated with weight gain.

I would recommend switching her to a single dose of a basal insulin analog at bedtime. NPH insulin can be switched to the basal insulin analog on a dose-for-dose basis, then upward-

Table 1 – Overview of case studies

Name	Age	Weight (kg)/ BMI (kg/m²)	Other clinically relevant findings	Current therapy	HbA_{1c} (%)	FBG (mg/dL)	PPG (mg/dL)
Kimberley	48	92/38.2	•Obese •Possible depression	•Metformin BID (1000 mg) •Sitagliptin (100 mg QD) •Basal insulin BID	8.4	180	—
Robert	52	89/27	•Healthy	•Metformin BID (total dose, 2500 mg) •Glimepiride (6 mg) •Basal insulin QD	8.2	120	260
Donald	56	77/24	•Healthy	•Metformin BID (1000 mg) •Repaglinide (2 mg TID) •Acarbose (50 mg TID) •Basal insulin QD	7.4	120	180
Mary	86	65/26	•Frail •History of CV disease •Arthritis •Moderate retinopathy •Impairment of manual dexterity	•BID premixed insulin	7.7	140	130 - 260

BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; FBG, fasting blood glucose; PPG, postprandial glucose; OADs, oral antidiabetic drugs; CV, cardiovascular.

ly titrated until the target FBG has been reached. Kimberley's concerns about weight gain can be addressed in part by using insulin detemir, which has been shown to be associated with less weight gain than either NPH insulin or insulin glargine.[8-10]

Kimberley should also be encouraged to participate in an educational program in order to learn more about the importance of managing her disease effectively. This may increase her sense of control over her diabetes and enable her to look after herself better whilst playing a more active role in her treatment. Evidence suggests that educational intervention can play a key role in lowering blood glucose levels.[11,12]

Case Study 2: Robert

Robert, a 52-year-old man, received a diagnosis of type 2 diabetes 11 years ago. Metformin was started, and glimepiride was added 3 years later when his HbA_{1c} was above goal. He started basal insulin (insulin glargine) 2 years ago and currently takes 38 units at bedtime. Robert has been conscientious about his treatment regimen and has a strong sense of routine. A typical day involves a morning run followed by a large breakfast, a sandwich at work during the day, and an evening meal with his family.

Robert is anxious about self-injecting in front of his colleagues during the working day, since many of them are unaware that he has diabetes. Since starting insulin therapy, he has struggled to maintain a weight of 89 kg (BMI of 27 kg/m^2) and is concerned about the possibility of gaining more weight if his regimen is changed. However, Robert's glucose control has deteriorated during the past 6 months. His HbA_{1c} has increased to 8.2% even though his FBG concentration (measured after his morning run) has been around 120 mg/dL. His PPG levels have also been elevated, particularly after breakfast and supper, when they can reach as high as 260 mg/dL. Robert would still like to inject insulin at home and would like minimal "disruption" to his life if he does have to intensify his insulin regimen, which is clearly indicated.

Recommendation. Robert's elevated PPG indicates that his physician needs to address his mealtime blood glucose levels, and that prandial insulin should be added to his treatment regimen. Robert would prefer to take insulin at home and is happy to continue with his relatively consistent meal plan and exercise regimen. Titrating his basal dose without addressing prandial insulin requirements is not likely to improve his overall glycemic control,[13] so switching him to a premixed insulin is an option. I would suggest starting him on a premixed insulin analog and would stop sulfonylureas, since he would now be taking a prandial insulin. Robert could continue to take his metformin as before.[3] Since his mealtimes are consistent, it would be straightforward for him to take one premixed dose before breakfast and another before dinner. In order to initiate the premixed dose, his current total basal insulin dose should be decreased by 10% to minimize the risk of hypoglycemia, split equally between the 2 mealtimes, then titrated upwards in increments of 2 IU until an FBG target of 80 to 130 mg/dL and a PPG target of 140 to180 mg/dL are met.

Lifestyle considerations	Recommended regimen
•Reluctant to make significant lifestyle changes	•Increased support from diabetes networks to encourage active management of regimen •Titrate insulin dose upward 10 IU until target of 160 mg/dL is reached •Review metformin dose (titrate to 2000 mg)
•Regular mealtimes •Reluctant to self-inject at work •Healthy lifestyle	•Stop sulfonylurea •Switch to premixed insulin, on a BID regimen taken at the 2 largest meals •Monitor metformin •Add third premixed dose as and when necessary
•Active lifestyle •Exercise and diet followed •Capable of following a complex regimen •Well-informed	•Stop OADs •Initiate basal-bolus therapy with 1 prandial injection at each mealtime •Monitor carefully
•Dependent on caregivers to administer insulin injections •Regular, healthy meals •Little exercise	•Add an additional premixed dose at the second largest meal of the day •Consider adding a third dose if this fails to address rising blood glucose levels

Case Study 3: Donald

Donald, a 56-year-old man, has played an active role in the management of his diabetes since the disease was first diagnosed 9 years ago. While he was initially able to control his blood glucose levels with diet and exercise alone, he needed to start pharmacological therapy within a year in order to maintain excellent glucose control, and additional medications were required over time. Metformin was started, and repaglinide and acarbose were added to his regimen later. Basal insulin was started 18 months ago, and his HbA_{1c} decreased from 7.8% to 6.8%.

Over the past few months, however, he has noted an increase in PPG, and his most recent HbA_{1c} was 7.4%. Donald continues to pay close attention to his caloric intake and visits a gym regularly. Donald's weight is currently stable at 77 kg (BMI of 24 kg/m^2) and he is in good health. His current treatment regimen includes metformin (1000 mg BID), repaglinide (2 mg TID), acarbose (50 mg TID), and 30 units of insulin detemir at night before bed.

Donald is anxious to maintain control over his blood glucose levels, because he is well informed about the risk of diabetes complications. He self-adjusts his basal insulin dose to maintain an FBG concentration of 85 to 120 mg/dL. His PPG levels have been elevated, particularly after supper, which is his biggest meal of the day. When he eats out, his post-supper glucose is higher than when he eats at home, reaching levels as high as 200 mg/dL and 230 mg/dL. When he limits his carbohydrate intake at breakfast and lunch, Donald notes that his PPG is less than 180 mg/dL. Donald would like as flexible an insulin regimen as possible, since he cannot always eat meals at the same time each day, and he is comfortable with the concept of injecting insulin multiple times per day.

Recommendation. Donald is clearly able to cope with basal-bolus therapy. Since his highest glucose measurement of the day is after dinner (provided he limits his carbohydrate intake at breakfast and lunch), his physician could simply add a rapid-acting insulin analog before supper, and continue all other treatments. If Donald wishes to eat more carbohydrates at breakfast and lunch, however, he should consider taking the rapid-acting analog before each meal.

Ideally, he should learn advanced carbohydrate counting and adjust his dose of prandial insulin with each meal based on the amount of carbohydrates he has eaten. This would give him the most flexibility and enable him to control glucose concentrations more effectively when he eats out. In order to implement this, he should stop oral medications other than metformin, decrease his basal insulin dose by 10%, and start prandial insulin with each meal.

Donald should initially be consistent with his carbohydrate intake at meals, as he would start with a small dose of the rapid-acting analog (3 units, or 10% of his basal dose) with each meal and then titrate these doses to achieve PPG levels between 140 and 180 mg/dL or preprandial glucose levels between 85 and 120 mg/dL. Donald should continue to titrate the basal insulin in order to achieve his FBG target of 85 to 120 mg/dL. Monitoring his 7-point blood glucose profile for a week would enable Donald to predict where in his day he has the greatest need of insulin, and a controlled, calorie-counting approach would allow him to finesse his bolus dose of insulin.

Case Study 4: Mary

Mary, an 86-year-old woman, received a diagnosis of type 2 diabetes 12 years ago. She currently lives in a nursing home, where she receives her medications from her caregivers. In addition to an antihyperglycemic medication, Mary takes soluble aspirin, a statin, and an angiotensin-converting enzyme (ACE) inhibitor daily. Mary had a myocardial infarction 8 years ago, but she has recovered well and has no symptoms of active cardiovascular disease. A stress test done 6 months ago showed no reversible perfusion defects. She also has nonproliferative retinopathy but no known nephropathy or neuropathy. Mary's diet has always been healthy, and her weight (65 kg; BMI, 26 kg/m^2) has been constant for the past 5 years. She walks every day for 25 minutes.

Mary was started on metformin soon after diabetes was diagnosed, and glimepiride was added 2 years later. Her glucose control was stable until 5 years ago, when basal insulin was added to counteract rising HbA_{1c} and FBG levels (the latter peaking at 180 mg/dL). Two years ago, she was switched to a premixed insulin regimen with twice-daily dosing, and glimepiride was stopped.

Mary's glucose levels have recently begun to rise again. Her last measured HbA_{1c} level was 7.7%, and her blood glucose profile shows moderate hyperglycemia throughout the day, ranging from 130 to 260 mg/dL, with postprandial spikes corresponding to her mealtimes. Her FBG readings over the past month have averaged 140 mg/dL. However, when she has had a smaller lunch than usual, her glucose levels drop into the 50 mg/dL range at about 4 PM.

Recommendation. Mary would benefit from intensification of her regimen. Her mealtimes are regular, enabling her caregivers to predict which are the most calorific in her day. She will need some help with her regimen, but her caregivers could assist with administration and dosing of insulin. She is already on a twice-daily premixed insulin regimen, and could add a third injection of premixed insulin at lunch or switch to a basal-bolus regimen.

A clinical study exploring intensification using premixes suggests that

Table 2 – Factors influencing choice of intensification regimen

Factor	Premixed regimen	Basal-bolus regimen
Patient dependence on physician/caregiver support	✔	
Patient has unpredictable caloric distribution between meals		✔
Patient is able to follow a complex regimen		✔
Patient has poorly controlled blood glucose levels—maximum efficacy required in regimen		✔
Patient wants flexibility in the daily routine		✔
Patient wants to minimize daily injections	✔	
Patient wants to keep regimen simple	✔	

optimization can be achieved by taking up to 3 injections of premixed insulin (1 with each meal).[14] In the 1-2-3 Study, investigators intensified patients from 1 to 2 to 3 injections of premixed insulin if they did not achieve therapeutic targets (based on fasting and pre-supper glucose and HbA_{1c} levels). Almost 80% of subjects achieved HbA_{1c} lower than 7% by the end of the study.[15] If the premixed insulin regimen does not achieve Mary's therapeutic goals, her caregivers could consider switching her to a basal-prandial regimen using analog insulins.

CONCLUSION

Intensifying insulin therapy requires a balance between following best practice guidelines and adapting current thinking to the specific requirements of an individual patient. No matter how much clinical trial data there are to substantiate a particular regimen, if patients are unwilling or unable to adhere to the prescribed treatment, their glycemic control may well remain suboptimal. Conversely, when patients are enthusiastic about managing their diabetes, and see the benefits of adhering to their regimen in terms of improved blood glucose levels and enhanced well-being, a successful partnership between patient and practitioner can be achieved. The patients selected for these case studies (**Table 1** and **Table 2**) reveal the diversity of needs and personality types that may confront a primary care physician. They also provide an example of how treatment can effectively address the patient's choice of therapy and lifestyle needs while satisfying the need to follow evidence-based principles of diabetes management. ■

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