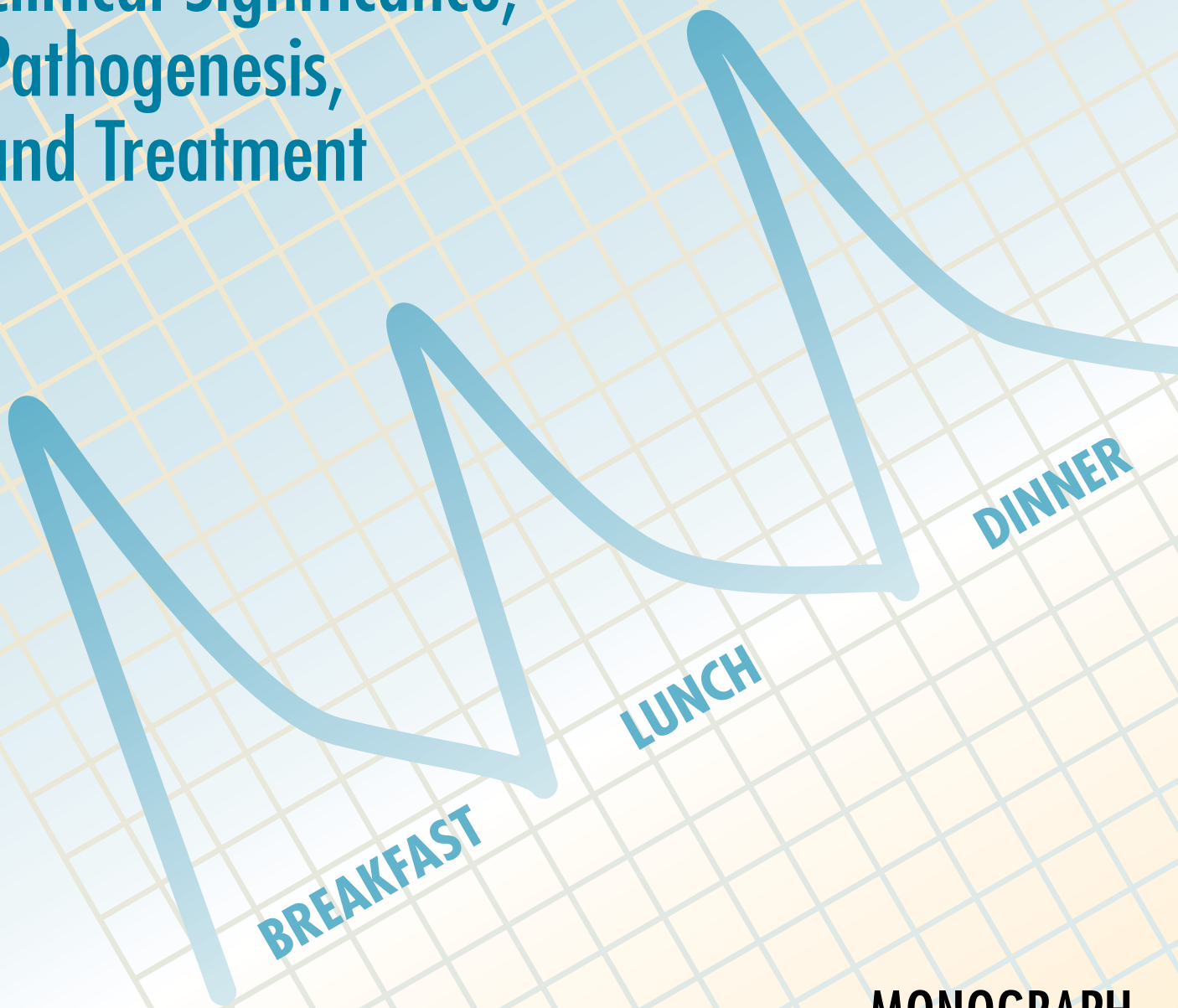
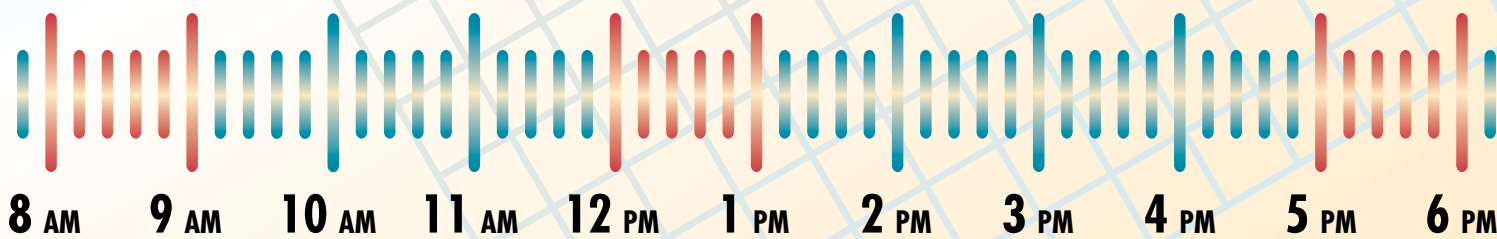


POSTPRANDIAL HYPERGLYCEMIA:

Clinical Significance,
Pathogenesis,
and Treatment



MONOGRAPH



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POSTPRANDIAL HYPERGLYCEMIA: CLINICAL SIGNIFICANCE, PATHOGENESIS, AND TREATMENT

Introduction

Although numerous national and international initiatives have been aimed at improving prevention, detection, and treatment of diabetes, the number of new cases has continued to accelerate. The rapidly rising increases in obesity and diabetes will lead to significant morbidity and mortality among broad populations. Worldwide, 246 million people have diabetes,¹ and the World Health Organization estimates that this number will grow to 366 million by 2030.² The International Diabetes Federation estimated that diabetes resulted in 3.8 million deaths worldwide in 2007 (approximately 6% of total global mortality).³ The worldwide direct costs for the treatment of diabetes in 2007 were estimated at \$232 billion and the minimum estimate for 2025 is \$302.5 billion.³

The burden of diabetes on individuals and society is, in large measure, due to its long-term microvascular and macrovascular complications.^{3,4}

Hyperglycemia and Diabetes Complications

A large number of epidemiologic studies have documented the strong link between chronic hyperglycemia, typically reflected by glycosylated hemoglobin (A1C), and long-term morbidity and mortality in patients with diabetes. Results from a cohort of 879 individuals with type 1 diabetes who were followed for 20 years indicated that A1C was significantly associated with all-cause and cardiovascular mortality. Subjects were divided into quartiles based on A1C. The risk of death for subjects in the highest quartile (average A1C 11.4%) was 2.42 times that for those in the lowest quartile (average A1C 8.7%). A similar pattern was seen in the risk of cardiovascular mortality for subjects in the highest quartile, which was 3.28 times that for subjects in the lowest A1C quartile.⁵

The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study also documented the relationship between A1C and cardiovascular morbidity and mortality. This study included 4,662 men and 5,570 women who had A1C and cardiovascular disease risk factors that were assessed from 1995 to 1997, and cardiovascular disease events and mortality evaluated during a follow-up period that ended in 2003.⁶ Subjects with A1C <5% had the lowest rates of cardiovascular disease and mortality. An increase in A1C of 1% was associated with a relative risk of death from any

cause of 1.24 in men and 1.28 in women. Results from this study also showed that the risks of cardiovascular disease events were 5 and 8 times higher for men and women, respectively, with A1C \geq 7.0% than for those with A1C <5%.⁶ The Atherosclerosis Risk in Communities (ARIC) study established a significant relationship between A1C and the risk of peripheral arterial disease in 1,894 middle-aged adults with diabetes. This study showed that subjects in the highest tertile for A1C (>7.5%) had a 6.3-fold increased risk of intermittent claudication and a 4.4-fold increased risk of hospitalization, amputation, or revascularization related to peripheral arterial disease versus those in the lowest tertile (A1C <5.9%).⁷ The results from this cohort also showed that A1C was positively correlated with risk of ischemic stroke and heart failure. The relative risks of stroke for subjects without and with diabetes in the highest tertile for A1C were 1.75 and 3.46, respectively, compared with the lowest A1C tertile of adults without diabetes.⁸

Meta-analyses of observational studies also support the finding that hyperglycemia is associated with an increased risk of cardiovascular disease in individuals with diabetes. In an evaluation of prospective cohort studies with data on A1C levels and incident cardiovascular disease that included 1,688 patients with type 1 diabetes and 7,435 patients with type 2 diabetes, a 1% increase in A1C was associated with an 18% rise in cardiovascular risk for subjects with type 2 diabetes and a 15% increase for those with type 1 disease.⁹ Results from the ARIC study indicated that the risk of heart failure increased by 20% for each 1% increase in A1C among subjects without coronary heart disease at baseline and by 14% among subjects with a history of coronary heart disease.¹⁰

Epidemiologic studies also have demonstrated that hyperglycemia increases the risk of microvascular complications. Investigators for the Pittsburgh Epidemiology of Diabetes Complications Study calculated hyperglycemia exposure in A1 months (A1C units above normal \times months) in 353 patients with insulin-dependent diabetes mellitus. They found that the risks of developing proliferative retinopathy, microalbuminuria, overt nephropathy, and distal symmetrical polyneuropathy all rose with increasing A1 months. Subjects with \geq 1,000 A1 months appeared to be at increased risk for developing most microvascular complications; however, the majority of complications arose in individuals with less exposure.¹¹ Results from the ARIC study showed that the risk of chronic kidney disease increases progressively with A1C. In this study, A1C concentrations of 6% to 7%, 7% to 8%, and >8% were associated with hazard ratios for chronic kidney disease of 1.4 \times , 2.5 \times , and 3.7 \times , respectively, versus an A1C <6%.¹²

The results summarized here indicate a strong correlation between A1C and microvascular and macrovascular events. However, they do not necessarily indicate a causative relationship between hyperglycemia and the vascular complications of diabetes. Large-scale interventional studies have provided convincing evidence that lowering A1C decreases the risk of adverse clinical outcomes in patients with type 1 diabetes.

Tight Glycemic Control and Reduction of Diabetes Complications

The definition for tight glycemic control has varied in clinical trials, but an A1C value <7% has been set as the target for treatment by the American Diabetes Association (ADA).¹³ It is important to note that this value is substantially higher than the average A1C for people without diabetes.¹⁴

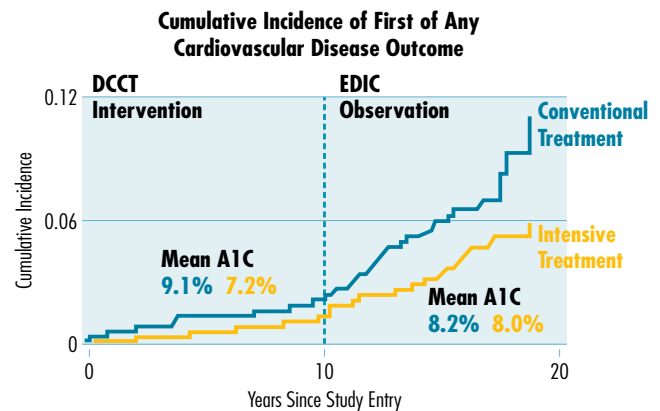
Landmark Studies

Studies have demonstrated the benefit of achieving and maintaining tight glycemic control to avoid, delay, and/or decrease the severity of the long-term complications of diabetes.¹⁵⁻¹⁸ These studies demonstrated the benefit of intensive treatment on microvascular outcomes as well as the benefit of reducing macrovascular complications.

The benefits of tight glycemic control demonstrated in the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) have proved to be long-lasting. Results from the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that intensive insulin treatment in patients with type 1 diabetes (as defined in DCCT) significantly decreased the risk of any cardiovascular disease event by 42% and the risk of the composite outcome of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% over 17 years of follow-up (**Figure 1**).¹⁹ Importantly, these benefits were realized despite the fact that A1C was 7.9% in the intensive treatment group and 7.8% in the conventional treatment group at the end of follow-up.¹⁹

The finding that the benefit of intensive antidiabetic therapy remained apparent over 10 years after the termination of DCCT/EDIC, even when patients in the 2 treatment groups had equivalent A1C values at the end of long-term follow-up, has raised the possibility that a period of intensive antidiabetic therapy results in “glycemic memory” that decreases cardiovascular risk even after the end of treatment.²⁰

Figure 1. Cumulative Risks of Any Cardiovascular Disease Event in Patients Who Received Conventional or Intensive Treatment in DCCT/EDIC¹⁹



Adapted with permission from Nathan DM, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med.* 2005;353:2643-2653. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Results from UKPDS also support the finding that a finite period of intensive antidiabetic therapy may produce longer term benefits with respect to the risk of complications from diabetes. In post-trial monitoring that occurred at the end of the 10 years of follow-up (5 years after the trial’s end, with no attempt to keep patients on assigned therapy), patients in the intensive treatment group had significant reductions in risk of any diabetes-related endpoint (−9%; $P=0.04$), microvascular disease (−24%; $P=0.001$), myocardial infarction (−15%; $P=0.001$), and death from any cause (−13%; $P=0.007$) versus patients who received conventional treatment. These benefits were observed despite an early loss of between-group differences in glycemic control that occurred by 1 year after the end of the trial.²¹

Increased Understanding of Treatment Benefits: Recent Clinical Results

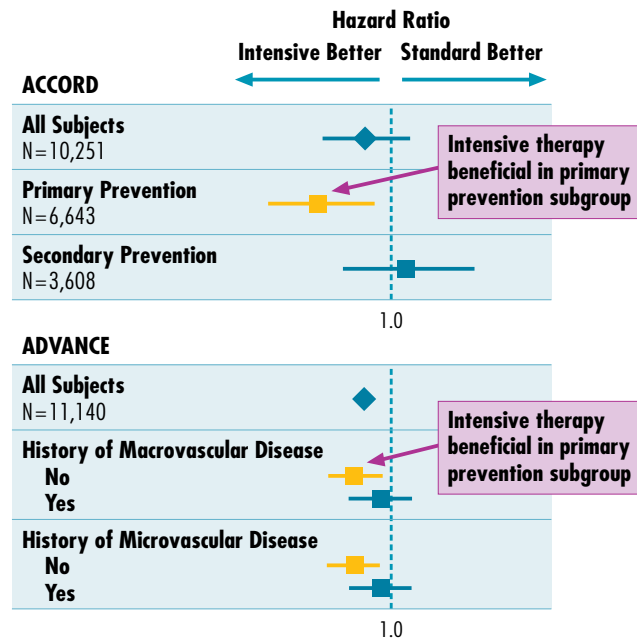
Although landmark studies have demonstrated substantial benefits of tight glycemic control in patients with type 1 or 2 diabetes, intensive insulin therapy reduces A1C more than conventional therapy; however, this is not always associated with decreased risk and better clinical outcomes for patients with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 10,251 patients with type 2 diabetes to comprehensive intensive therapy with a target A1C of <6% or standard therapy with a target A1C of 7.0% to 7.9%. Results from ACCORD showed that patients receiving intensive therapy achieved an average A1C of 6.4% versus 7.5% for patients receiving standard therapy. However, intensive therapy was associated with an increased risk of death (hazard ratio, 1.22; 95% confidence

interval, 1.01 to 1.46; $P=0.04$) from any cause, cardiovascular mortality, and nonfatal myocardial infarction compared with standard therapy.²² The writing group for ACCORD could not identify an explanation for the mortality findings.

Two recent studies also have indicated that intensive antidiabetic therapy does not decrease cardiovascular events or mortality in patients with diabetes. The Action in Diabetes and Vascular Disease (ADVANCE) study included 11,140 patients with type 2 diabetes who were randomized to intensive therapy with an A1C goal of $\leq 6.5\%$ or to standard therapy. At the end of the follow-up period, A1C levels in the intensive and standard therapy groups were 6.5% and 7.3%, respectively, and the combined incidences of microvascular and macrovascular events were 18.1% and 20.0%, respectively, with a significant difference favoring intensive therapy. Intensive therapy also significantly reduced microvascular events (9.4% versus 10.9%), but not macrovascular events (10.0% versus 10.6%).²³ The Veterans Affairs Diabetes Trial (VADT) included 1,791 patients with uncontrolled type 2 diabetes and assigned them to intensive glucose control with an A1C target of $< 6.0\%$ or to standard glucose control ($< 9.0\%$).²⁴ The primary study endpoint was a composite of cardiovascular events (ie, myocardial infarction, cardiovascular death, stroke, revascularization, hospitalization for heart failure, amputation for ischemia). After 6.5 years of treatment, A1C was 6.9% in the intensive therapy group and 8.4% in the standard therapy group. No significant between-group differences were observed for the primary endpoint, cardiovascular death, death from any cause, or the occurrence of any microvascular outcomes (eg, ophthalmologic disorders, nephropathy, new neuropathy).²⁴

The ADA, American Heart Association (AHA), and American College of Cardiology (ACC) recently evaluated the results from ACCORD, ADVANCE, and VADT and how these studies might influence treatment recommendations for patients with diabetes.²⁵ Their evaluation indicated that intensive glycemic control was beneficial in decreasing macrovascular complications in patients with a shorter duration of type 2 diabetes and without established atherosclerosis (**Figure 2**).^{22,23} Specifically, it was noted that ACCORD patients with no prior cardiovascular disease experienced a significant decrease in cardiovascular events and that intensive treatment in VADT patients with low baseline coronary aortic calcium scores resulted in significantly lower risk of the primary endpoint. In addition, patients with a long duration of diabetes, history of hypoglycemia, and advanced atherosclerosis may not derive significant benefit from intensive glycemic control.²⁵

Figure 2. Benefits of Aggressive Therapy Aimed at Tight Glycemic Control in Primary Prevention of Events: The ACCORD²² and ADVANCE²³ Studies



Adapted with permission from The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559 and The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560-2572. Copyright © 2008 Massachusetts Medical Society. All rights reserved.

The position stated by the ADA and a scientific statement of the ACC Foundation and the AHA have established an A1C $< 7\%$ as the goal of antihyperglycemic therapy in patients with type 1 or 2 diabetes and in patients with diabetes and comorbid coronary or other atherosclerotic vascular disease.^{13,26} Review of results from ACCORD, ADVANCE, and VADT by Skyler et al reaffirmed an A1C $< 7\%$ as the treatment goal for patients with diabetes (**Table 1**), as did the DCCT and UKPDS results, which noted that therapy aimed at lowering A1C to $< 7\%$ soon after diagnosis decreased the risk of macrovascular complications. They stated further that the ACCORD, ADVANCE, and VADT results do not suggest the need for major changes in the targets for antidiabetic therapy.²⁵ These conclusions are consistent with the findings from the meta-analysis of 10 prospective cohort studies of patients with type 2 diabetes and 3 prospective cohort studies of patients with type 1 diabetes in which chronic hyperglycemia was associated with an increased risk of cardiovascular disease.⁹

Landmark study results clearly show that elevated A1C is strongly associated with an increased risk of microvascular diabetes complications and that treatment aimed at lowering A1C reduces the long-term risk of complications. Long-term follow-up from these studies has suggested that A1C levels around 7.0% are associated with a reduced risk of macrovascular

disease. The ACCORD, ADVANCE, and VADT studies have refined our understanding of the benefits of tight glycemic control by demonstrating that aggressive treatment may lead to reduction in the risk of complications in primary prevention but may be less effective in patients with long-standing diabetes and/or evidence of microvascular or macrovascular disease.

Table 1. A1C Targets Recommended by the ADA, AHA, and ACC²⁵

	A1C Goal	ADA	ACC/AHA
Microvascular disease	<7.0%*	A-level	Class I Evidence level A
Macrovascular disease	<7.0%†	B-level	Class IIb Evidence level A

* Nonpregnant adults in general.

† General goal of <7% appears reasonable.

Fasting and Postprandial Plasma Glucose

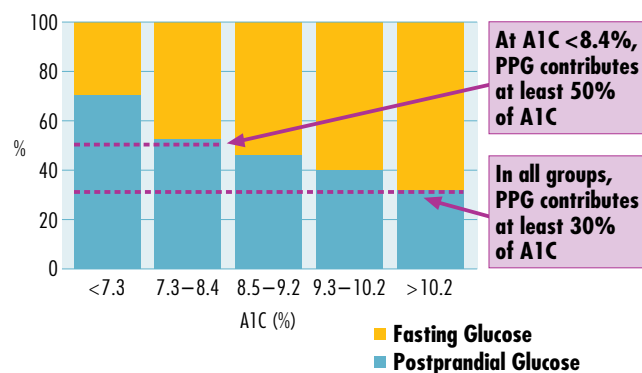
The recent landmark studies focused on the relationship between A1C and microvascular and macrovascular complications in diabetes. However, it is important to remember that A1C is determined by 2 factors: fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Moreover, the contributions of each of these measures to A1C vary with the degree of glycemic control among patients with diabetes.

Contributions of FPG and PPG to A1C

A seminal study by Monnier and colleagues assessed the diurnal glycemic profiles of 290 patients with type 2 diabetes and different levels of A1C while fasting and after meals. Areas under the curve above FPG concentrations (AUC_1) and $AUC > 110$ mg/dL (AUC_2) were calculated to determine the relative contributions of PPG (AUC_1/AUC_2 , %) and FPG ($[AUC_2 - AUC_1]/AUC_2$, %) to overall diurnal hyperglycemia. These results were then evaluated over quintiles of A1C. Results from this analysis indicated that the relative contribution of PPG to A1C increased progressively from highest to lowest A1C quintiles (**Figure 3**). In patients with A1C levels in the 7.3% to 8.4% range, PPG contributed $\geq 50\%$ of the A1C. In patients with A1C levels greater than 8.5%, FPG contributed more than PPG; however, even at high A1C levels ($>10.2\%$), PPG contributed at least 30% toward the A1C.²⁷

Postprandial glucose levels significantly contribute to A1C in all patients, and this contribution increases at lower A1C levels

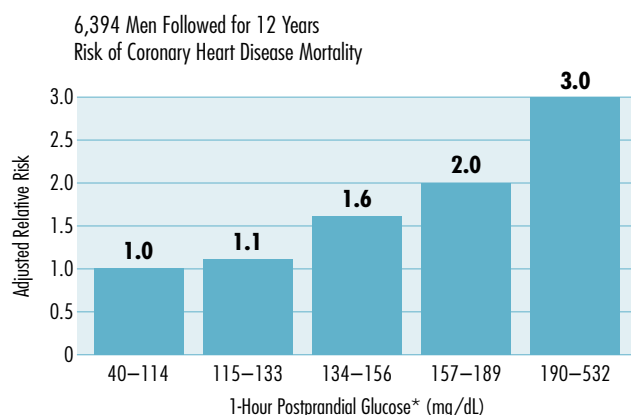
Figure 3. Relative Contributions of PPG and FPG to Overall Diurnal Hyperglycemia Over Quintiles of A1C²⁷



Contributions of FPG and PPG to Risk of Diabetes Complications

Both FPG and PPG have been shown to be significant independent predictors of long-term complications in patients with diabetes. Multiple large-scale studies have demonstrated significant relationships between elevated FPG and increased risk of cardiovascular disease, cerebrovascular events, nephropathy, end-stage renal disease, and death.²⁸⁻³⁰ PPG is believed to be a particularly important determinant of macrovascular risk. The Honolulu Heart Program showed that 1-hour PPG is a strong predictor of risk of coronary heart disease mortality. This study included 6,394 men who had PPG evaluated 1 hour after a 50-g glucose challenge and who were then followed for 12 years for the occurrence of fatal coronary heart disease and nonfatal myocardial infarction. Study results showed that the risk of fatal coronary heart disease increased progressively with rising 1-hour PPG (**Figure 4**), as did the combined endpoint of fatal coronary heart disease and nonfatal myocardial infarction.³¹

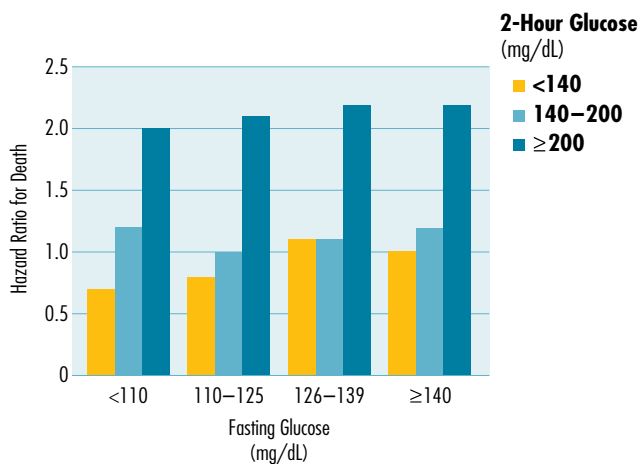
Figure 4. Relationship Between 1-Hour PPG and Risk of Coronary Heart Disease Mortality in the Honolulu Heart Program³¹



* 1 hour after randomly timed 50-g oral glucose challenge.

The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study underscored the independent effect of PPG on mortality risk in patients with diabetes. In this study, baseline data for FPG and PPG concentrations were captured for 18,048 men and 7,316 women 2 hours after a 75-g glucose challenge. A significant positive correlation was shown between 2-hour PPG and mortality, and this relationship remained apparent for each stratum of FPG ranging from <110 to ≥ 140 mg/dL (**Figure 5**).³²

Figure 5. Relationship Between Mortality Risk and 2-Hour PPG Across Strata of FPG in DECODE³²



Other epidemiologic studies also have demonstrated the importance of PPG as a risk factor for the development of diabetes complications. In the Oslo Study, nonfasting PPG levels were predictors of fatal stroke in patients with diabetes, and stroke risk increased by 13% for each 18 mg/dL elevation in PPG.³³ The Diabetes Intervention Study, an 11-year follow-up of 1,139 patients with newly diagnosed type 2 diabetes, indicated that PPG, but not FPG, was a significant predictor of mortality.³⁴ The San Luigi Gonzaga Diabetes Study, which enrolled 284 men and 245 women with type 2 diabetes, also showed that PPG, but not FPG, was a significant independent risk factor for cardiovascular events.³⁵

These study results are consistent with those from a meta-regression analysis of 95,783 subjects who were followed for 12.4 years. The analysis showed that an FPG of 110 mg/dL and a 2-hour PPG level of 140 mg/dL were associated with relative risks of cardiovascular events of 1.33 and 1.58, respectively, versus a glucose level of 75 mg/dL.³⁶

Linking FPG and PPG to Diabetes Complications: Mechanisms

Hyperglycemia may contribute to atherosclerosis and an increased risk of diabetes complications via multiple mechanisms.

One possible mechanism in the development of atherosclerosis is a non-enzymatic reaction between glucose and proteins or lipoproteins in arterial walls that results in the formation of advanced glycation end products (AGEs). Accumulation of AGEs in blood vessel walls may lead to the development of atherosclerosis; AGEs may interact with AGE receptors (RAGEs) to promote other actions that contribute to the development and progression of atherosclerosis (**Table 2**).³⁷

Table 2. Atherosclerosis-Promoting Effects of AGEs: Nonreceptor- and Receptor-Mediated Mechanisms³⁷

Nonreceptor Mediated	
Extracellular matrix	<ul style="list-style-type: none"> Collagen cross-linking Enhanced synthesis of extracellular matrix components Trapping of low-density lipoprotein (LDL) in the subendothelium Glycosylated subendothelial matrix quenching nitric oxide
Functional alterations of regulatory proteins	<ul style="list-style-type: none"> Fibroblast growth factor β glycosylation reduces its heparin binding capacity and its mitogenic activity on endothelial cells Inactivation of the complement regulatory protein CD59
Lipoprotein modifications	<ul style="list-style-type: none"> Glycosylated LDL Reduced LDL recognition by cellular LDL receptors Increased susceptibility of LDL to oxidative modification
Receptor Mediated	
Promoting inflammation	<ul style="list-style-type: none"> Secretion of cytokines such as tumor necrosis factor-α and IL-1 Chemotactic stimulus for monocyte-macrophages
Induction of cellular proliferation	<ul style="list-style-type: none"> Stimulation of platelet-derived growth factor and insulin-like growth factor-1 from monocytes and possibly smooth muscle cells
Endothelial dysfunction	<ul style="list-style-type: none"> Increased permeability of endothelial cell monolayers Increased procoagulant activity Increased expression of adhesion molecules Increased intracellular oxidative stress

Adapted with permission from Aronson and Rayfield.³⁷

Stimulation of protein kinase C by hyperglycemia also may contribute to microvascular and macrovascular abnormalities via increased expression of transforming growth factor β , which results in thickening of the capillary basement membrane. Hyperglycemia also increases oxidative stress via free radical production and AGEs.³⁷

Elevation of intracellular glucose levels may stimulate the aldose reductase pathway. Excess activation of this enzyme may lead to depletion of nicotinamide adenine dinucleotide phosphate, which is involved in the formation of sorbitol from glucose. In addition, the decline in cellular nicotinamide adenine dinucleotide phosphate may result in decreased expression of nitric oxide by endothelial cells and endothelial dysfunction.^{38,39}

Why PPG is closely linked with increased cardiovascular risk is not known, but recent research has suggested several possibilities similar to those mentioned above. Postprandial hyperglycemia is associated with increased oxidative stress that may result from development of AGEs, stimulation of the polyol pathway, and activation of protein kinase C. Elevated oxidative stress may lead to or worsen impairment in endothelial function, which is an early step in the progression of atherosclerosis. Oxidative stress associated with elevated PPG also may decrease levels of nitric oxide, which may lead to increased expression of nuclear factor- κ B, resulting in elevation of pro-inflammatory cytokines and growth factors that contribute to the development of atherosclerosis. Elevated PPG and the resultant oxidative stress also may increase the risk of thrombosis via activation of platelets and increased thrombin generation.⁴⁰ Excessively elevated PPG levels may elicit changes in the function of mesangial cells, pericytes, smooth muscle cells, and macrophages, increasing the risk of cardiovascular events.⁴¹

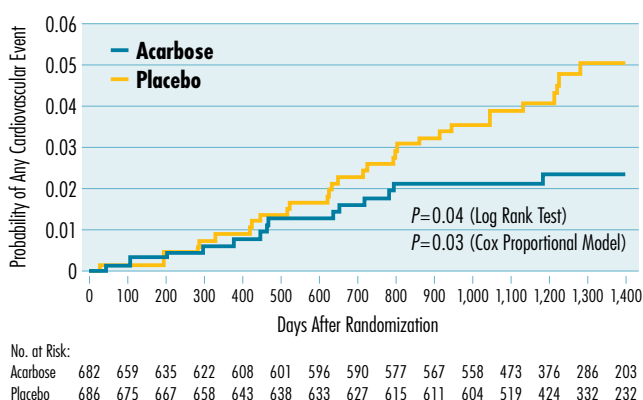
Targeting PPG to Reduce Diabetes Complications

Several studies have demonstrated the effectiveness of targeting PPG to decrease the risk of diabetes complications. The Campanian Postprandial Hyperglycemia Study compared the effects of repaglinide and glyburide on PPG, carotid intima-media thickness, and markers of systemic vascular inflammation in 175 patients with type 2 diabetes. After 12 months, peak PPG was 148 mg/dL in the repaglinide group versus 180 mg/dL in the glyburide group. Regression of carotid intima-media thickness (a decrease >0.020 mm) was observed in 52% of patients in the repaglinide group versus 18% of those in the glyburide group. Reductions in C-reactive protein and IL-6 were significantly greater with repaglinide than with glyburide. These results show that targeting PPG can promote atheroma regression in patients with type 2 diabetes.⁴²

The STOP-NIDDM study assessed the effectiveness of reducing postprandial hyperglycemia and the risks of hypertension and cardiovascular disease with the α -glucosidase inhibitor acarbose (100 mg TID with each meal) versus placebo in patients with

impaired glucose tolerance. The study followed 1,368 evaluable patients for an average of 3.3 years. The primary endpoints were cardiovascular events (ie, coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral vascular disease) and hypertension (blood pressure $\geq 140/90$ mm Hg). The decrease in PPG was associated with a 49% relative risk reduction in the occurrence of cardiovascular events (**Figure 6**) and a 91% decrease in the risk of myocardial infarction. Treatment with acarbose also resulted in a 34% decline in the relative risk for hypertension.⁴³

Figure 6. Effect of Mealtime Acarbose on the Probability of Remaining Free of Cardiovascular Disease⁴³



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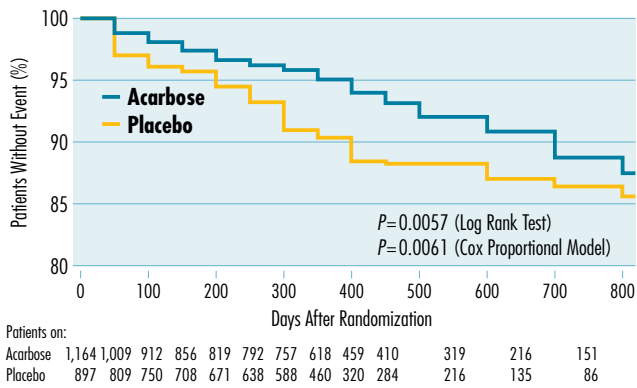
Additional analysis of the STOP-NIDDM results showed that acarbose significantly decreased the risk of silent myocardial infarctions revealed by echocardiography.⁴⁴

Meta-analysis of clinical trial results for patients with type 2 diabetes also supports the effectiveness of acarbose in decreasing cardiovascular risk. Seven randomized, double-blind, placebo-controlled studies with treatment durations ≥ 52 weeks were included in the analysis. In the studies, a total of 1,248 patients were treated with acarbose and 932 received placebo. The primary outcome measure for the meta-analysis was time to a cardiovascular event. Acarbose significantly decreased the risk of cardiovascular events by 35% ($P=0.0061$; **Figure 7**) and myocardial infarction by 64% ($P=0.012$) as well as A1C, FPG, and 1-hour and 2-hour PPG (all $P<0.001$) compared with placebo.⁴⁵

Both FPG and PPG are independent risk factors for diabetes complications, and postprandial hyperglycemia is a particularly potent risk factor for the development of macrovascular events, such as coronary heart disease. The mechanisms underlying deleterious vascular effects of elevated FPG and PPG are not completely understood, but they appear to be mediated by

multiple pro-inflammatory, procoagulant, and remodeling pathways that involve formation of AGEs, activation of protein kinase C, and oxidative stress.

Figure 7. Kaplan-Meier Survival Curve for the Time to Develop Any Cardiovascular Event During Treatment With Either Acarbose or Placebo⁴⁵

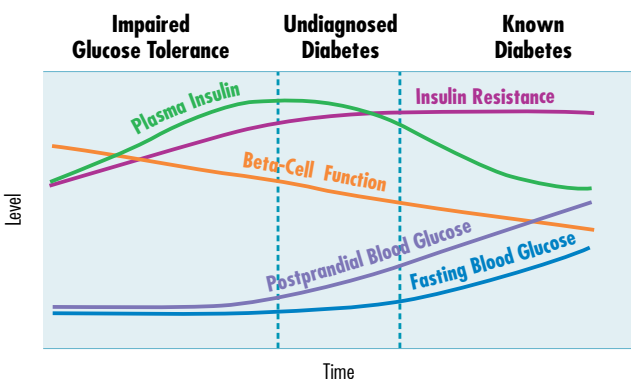


Reproduced from Hanefeld M et al, Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies, *European Heart Journal*, 2004;25:10-16, by permission of the European Society of Cardiology.

Natural History of Diabetes: Implications for Treatment

A sequence of metabolic events that ultimately results in type 2 diabetes usually precedes the hyperglycemia that leads to diagnosis of the disease by many years (Figure 8). Before the onset of diabetes, impaired glucose tolerance is associated with increasing insulin resistance, compensatory increases in insulin secretion, and modest increases in PPG. At this stage, FPG remains at near-normal levels. As pancreatic β -cells begin to fail, PPG, FPG, and hepatic glucose production rise. Eventually, β -cells are unable to compensate for rising insulin resistance and the resultant hyperglycemia marks the beginning of frank type 2 diabetes.⁴⁶

Figure 8. Natural History of Type 2 Diabetes⁴⁶



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β -Cell Dysfunction and Death

Although controversy exists regarding whether insulin resistance or impaired insulin secretion constitutes the primary defect in type 2 diabetes, current evidence supports β -cell function as the initial defect. Individuals with type 2 diabetes experience a gradual decline in insulin secretion that results from impairment of function and ultimately the death of pancreatic β -cells.⁴⁷ Individuals with type 2 diabetes have a progressive deterioration in β -cell function and mass and a pancreatic islet cell function of about 50% of normal at the time of diagnosis.⁴⁸ Two changes in β -cells contribute to the defect in insulin secretion characteristic of type 2 diabetes: a reduction in insulin secretion in response to glucose and decreased β -cell mass secondary to increased apoptosis of these cells.⁴⁷ Several factors, including glucotoxicity, lipotoxicity, and the effects of pro-inflammatory cytokines, are believed to contribute to the secretory deficit and abnormal apoptosis of β -cells.^{47,48}

Glucotoxicity

Glucose is a key regulator of insulin secretion and modulates the turnover of β -cells. Glucotoxicity has been defined as β -cell damage caused by chronic exposure to supraphysiological glucose concentrations. Glucotoxicity is associated with decreased insulin synthesis and secretion caused by decreased insulin gene expression. Once plasma glucose levels exceed a certain threshold in humans, β -cell apoptosis increases. It is important to note that sustained high glucose levels are not required for alterations in β -cell function and mass. Postprandial hyperglycemia may be sufficient for deleterious changes in β -cell function and turnover.⁴⁷

β -Cells are extremely sensitive to small changes in glucose levels. When glucose levels rise within the physiological range and are transient, β -cells respond by secreting insulin; however, when very high glucose levels are present for prolonged periods, these glucose levels may be sensed as a pro-apoptotic signal.⁴⁷ It has been suggested that the deleterious effects of sustained hyperglycemia on β -cells may include increased protein flux through the endoplasmic reticulum and resultant stress, elevated intracellular calcium levels, and generation of reactive oxygen species, which leads to chronic high oxidative stress. Reactive oxygen species, particularly hydroxyl radicals, decrease the transcription factor—pancreas duodenum homeobox-1—that promotes insulin gene expression and glucose-induced insulin secretion, which is also a regulator of β -cell survival.⁴⁹

Lipotoxicity

Elevations in circulating free fatty acids may be toxic to β -cells and contribute to their progressive loss in individuals with diabetes. Physiological increases in plasma free fatty acid concentrations in humans potentiate glucose-stimulated insulin secretion and are not believed to be lipotoxic, but they may contribute to progressive β -cell failure in some individuals with a genetic predisposition toward development of type 2 diabetes.⁴⁷

Inflammation

Individuals with diabetes have a chronic increase in expression and secretion of inflammatory mediators that may contribute to the dysfunction and loss of β -cells. Leptin, tumor necrosis factor- α , IL-6, and IL-1 may act on pancreatic islets and impair β -cell secretory function.⁴⁷

A combination of insulin resistance and β -cell dysfunction result in a progressive dysregulation of glucose homeostasis that leads to impaired glucose tolerance and subsequently frank diabetes. The primary and central defects in this progression are reduced insulin secretion by β -cells and a loss of β -cell mass. The reduced numbers of β -cells and their impaired function, along with progressive insulin resistance, result in elevated PPG that may be present well before diabetes is diagnosed; elevated FPG, which becomes apparent later in the disease course, may lead to the diagnosis of type 2 diabetes.

Development and Metabolic Consequences of Postprandial Hyperglycemia

The hypothesis that the dysfunction and death of pancreatic β -cells probably contribute to PPG have been supported by the studies mentioned in the preceding sections. However, other factors are also involved in the development of postprandial hyperglycemia. These include loss of early insulin response, hepatic and peripheral (muscle and fat) insulin resistance, excessive glucagon secretion, and accelerated gastric emptying. All of these dysfunctions lead to abnormalities in glucose and lipid homeostasis.

Loss of the early insulin response is a defect found in patients with type 1 and type 2 diabetes

Changes in Insulin Response With β -Cell Dysfunction

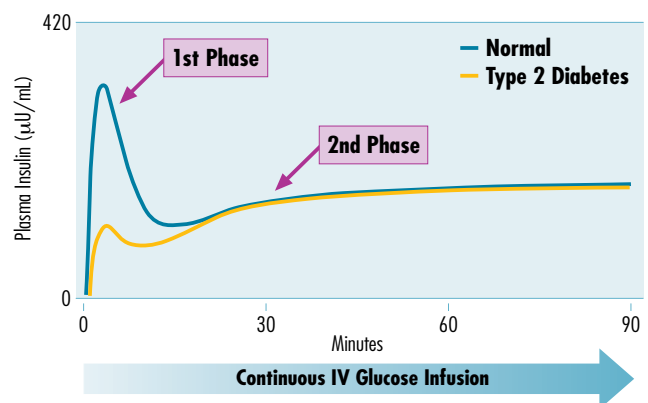
The normal pattern of insulin secretion in healthy individuals has 2 characteristic features. Basal insulin secretion occurs continuously to maintain steady glucose levels for extended periods between meals. Prandial insulin secretion is a rapidly occurring rise in plasma insulin concentrations that occurs in response to a meal; it returns to basal levels after 2 to 3 hours. Together, basal and prandial insulin secretion maintain blood glucose levels within the physiologic range over 24 hours.⁵⁰

Insulin Response to Glucose Challenge

The insulin response to a continuous infusion of intravenous glucose has 2 distinct phases (**Figure 9**). Insulin levels rise sharply within 3 to 5 minutes, peak in approximately 10 minutes, and then decline; this is known as the *first-phase insulin response*. This is followed by a more gradual and progressive increase in insulin levels that lasts as long as glucose is infused (i.e., the *second-phase insulin response*).⁵¹ The acute response to a glucose challenge is mediated by the direct insulinotropic effects of glucose, neural stimulation, and augmentation of the β -cell response by the incretin hormones⁵² and has an important role in glucose homeostasis. Most importantly, the first phase of insulin release strongly inhibits hepatic glucose production, a key determinant of PPG levels.⁵¹

The normal early insulin response rapidly suppresses, or “switches off,” hepatic glucose output, which prevents excessive postprandial glucose excursions

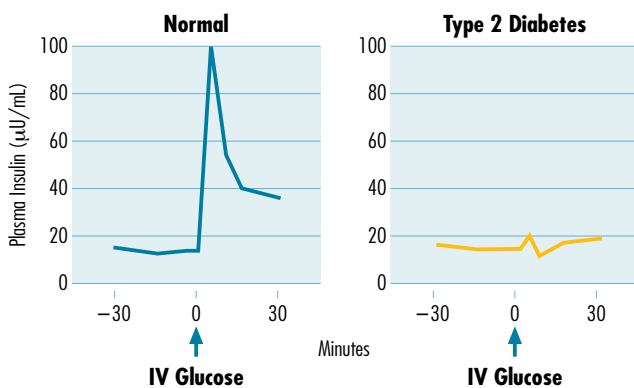
Figure 9. First- and Second-Phase Responses to Intravenous Glucose Administration⁵¹



Loss of Early Insulin Response in Diabetes

Results from studies conducted more than 35 years ago showed that loss of first-phase insulin response was a characteristic defect in insulin secretion in patients with diabetes. Assessment of responses to intravenous glucose administration in 10 normal subjects (ie, without diabetes) and 10 subjects with diabetes indicated that the rapid spike in serum insulin observed in response to 5-g glucose infused over 3 seconds was almost completely lost in those with diabetes (Figure 10).⁵³

Figure 10. Effect of Intravenous Glucose (5 g) Given Over 3 Seconds on Serum Insulin Levels in a Normal Subject (ie, Without Diabetes) and a Subject With Diabetes⁵³



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Loss of the early insulin response results in insufficient suppression of hepatic glucose output, which is a major cause of postprandial hyperglycemia in type 2 diabetes

Loss of early insulin secretion is believed to reflect initial adverse effects of hyperglycemia on β -cells.⁵⁴ Impairment of first-phase insulin secretion occurs early in the disease course and has been identified in patients with impaired glucose tolerance and impaired FPG. It also has been shown to be predictive of progression to overt type 2 diabetes.⁴⁸ Longitudinal studies have established that the transition from normal glucose tolerance to diabetes is associated with a progressive deterioration in early insulin response. In a study of 404 Pima Indian individuals with normal glucose tolerance who were followed for up to 5 years, progression to impaired

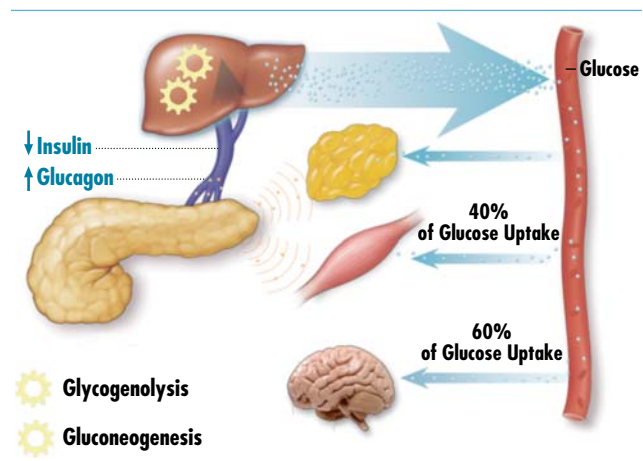
glucose tolerance was associated with a 27% reduction in the acute insulin response.⁵⁵ Further progression from impaired glucose tolerance to diabetes was accompanied by a further 51% decrease in this response.

A 7-year follow-up study of 667 elderly men without diabetes at the time of initial evaluation also demonstrated that an impaired early response to a glucose challenge was associated with an increased risk of diabetes. Overall, 7% of the subjects in this study developed diabetes, and the risk of diabetes increased among individuals in the lowest tertile for early insulin response.⁵⁶ Another 7-year follow-up of first-degree relatives of 33 individuals with type 2 diabetes showed that progression from normal to impaired glucose tolerance was associated with a 25% reduction in insulin response, reflecting a 38% decline in β -cell function.⁵⁷

Effects of Early Insulin Response

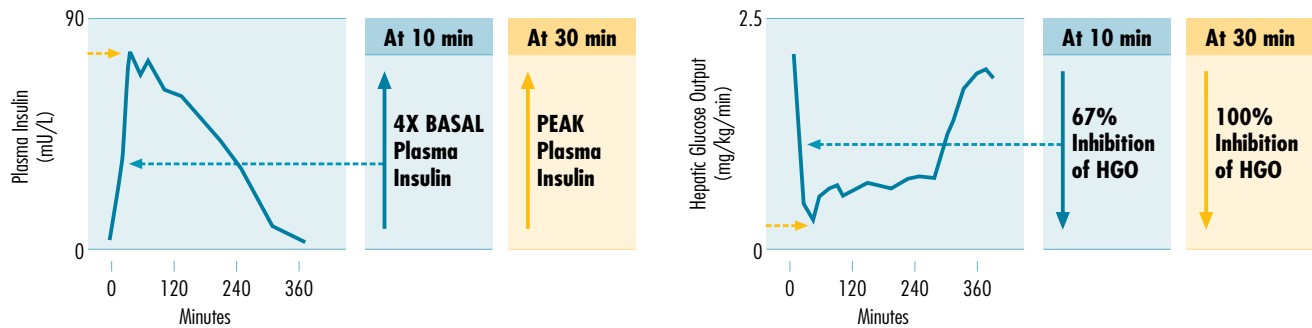
Early insulin response is critically important in controlling PPG and occurs primarily via its effect on hepatic glucose production. This early insulin response to glucose is enhanced by the concomitant action of incretins and neural responses to nutrient ingestion. It rapidly exposes the liver to elevated insulin levels that strongly inhibit hepatic glucose output, which is composed of both glucose synthesis (gluconeogenesis) and glycogen breakdown (glycogenolysis) (Figure 11).⁵¹

Figure 11. Effects of Early Insulin Response on Hepatic Glucose Production and Peripheral Glucose Disposal⁵¹



The early insulin response is a rapid release of insulin from β -cells in response to meal ingestion

Figure 12. Early Insulin Response Rapidly Suppresses Hepatic Glucose Output (HGO)⁵⁸



Taylor and colleagues demonstrated a close relationship between the early insulin response and suppression of hepatic glucose output (**Figure 12**). In this study of healthy volunteers, hepatic glucose output, plasma insulin, and glucagon levels were measured after ingestion of a mixed meal. Hepatic glucose output was suppressed by 67% within 10 minutes and completely inhibited by 30 minutes. This profound suppression was followed by a return to baseline levels 300 and 460 minutes after the meal. The suppression in hepatic glucose output was mirrored by a rapid rise in insulin levels, which peaked at 30 minutes after ingestion of the meal and declined to basal levels at 360 minutes.⁵⁸ Rapid delivery of insulin to the liver has been shown to be more effective than more gradual exposure for inhibiting glucose production.⁵¹

These results support the view that the early insulin response acts like a physiological switch that turns off hepatic glucose output. When this early response is lost, as in patients with diabetes, suppression of hepatic glucose production is compromised, resulting in elevated PPG levels characteristic of this disease.

The normal early insulin response has additional actions that contribute to preventing postprandial hyperglycemia. Both the first- and late-phase insulin responses to glucose stimulation contribute to the counter-regulatory effect of insulin on glucagon-stimulated hepatic glucose production. Studies in animals have shown that first-phase insulin release significantly inhibits glucagon-stimulated increases in plasma glucose, even in the absence of later phase insulin secretion.⁵¹ The early insulin response also may decrease PPG by facilitating more rapid uptake of glucose into peripheral tissues. Although a biphasic pattern of insulin levels is not observed in peripheral tissues following a glucose challenge (possibly due to the time required for insulin to cross the endothelial barrier), it has been suggested that early insulin secretion is still an important determinant of the rise in interstitial insulin concentration and glucose transfer into tissues.⁵¹

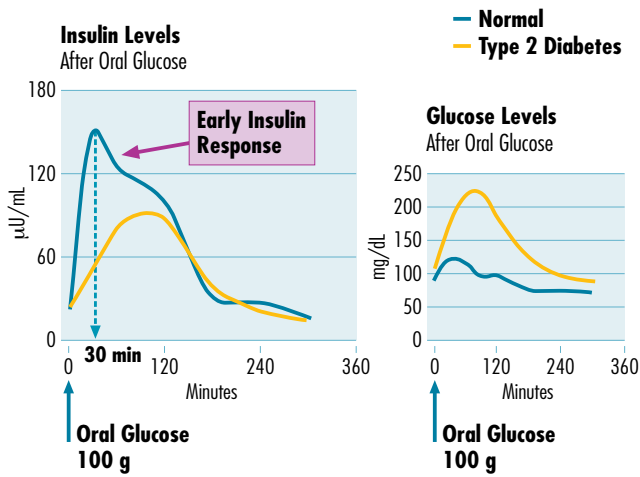
Consequences of Loss of Early Insulin Response

It is now evident that early insulin response is a critical factor in the rapid and efficient suppression of endogenous glucose production following a meal.⁵¹ The importance of the early insulin response in modulating PPG levels was demonstrated in a study that compared plasma insulin and glucagon responses in 15 subjects with impaired glucose tolerance and 16 normal controls.⁵⁹ After a 1-g/kg oral glucose challenge, total systemic appearance of glucose was significantly higher in subjects with impaired glucose tolerance versus controls, a difference that was due to reduced suppression of endogenous hepatic glucose production. Despite late hyperinsulinemia, subjects with impaired glucose tolerance had smaller increases in plasma insulin and fewer reductions in plasma glucagon at 30 minutes. These results support the conclusion that loss of early insulin response leads to decreased suppression of hepatic glucose production and postprandial hyperglycemia, which worsens to clinical hyperglycemia as the disease progresses.⁵⁹

A study of 62 healthy individuals (ie, without diabetes) and 35 patients with type 2 diabetes demonstrated the patterns of plasma and insulin concentrations and the effects of the loss of early insulin response (**Figure 13**). In the healthy individuals, early insulin response reached a peak at 30 minutes, followed by a return to baseline levels between 3 and 4 hours after oral glucose administration. PPG peaked less than 1 hour after glucose was administered. In the subjects with diabetes, early insulin response was lost and the peak PPG level was approximately twice that in the normal individuals.⁶⁰

Loss of early insulin response in patients with type 2 diabetes and the resulting hyperglycemia may contribute to the postprandial elevations in triglycerides and free fatty acid levels that have been linked to cardiovascular risk in patients with diabetes.⁶¹

Figure 13. Insulin and Glucose Responses in Normal Subjects and Subjects With Type 2 Diabetes⁶⁰

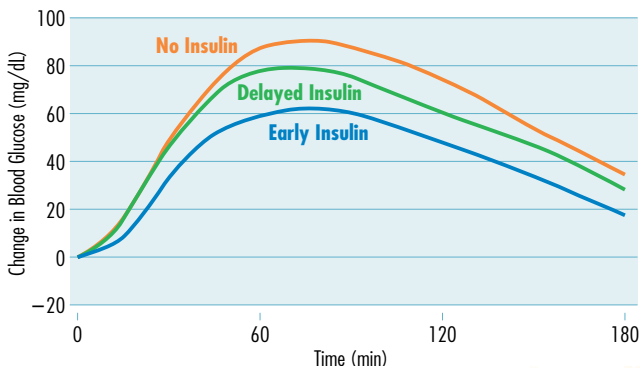


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Restoration of Early Insulin Response Reduces Postprandial Hyperglycemia

A study from more than 20 years ago demonstrated the importance of the timing of early insulin response in maintaining normal PPG levels. Bruce et al demonstrated the importance of this response by administering exogenous intravenous insulin (1.8 U over 30 minutes) to 8 subjects with type 2 diabetes in 3 different ways: 1.8 U delivered over 30 minutes at the time of a standard breakfast; the same dose delayed by 30 minutes; and the same dose administered over 180 minutes. Delivery of insulin with no delay in a manner that mimicked the normal early response resulted in a 33% reduction in the glycemic response to the meal and blood glucose levels that were still reduced after 180 minutes (Figure 14).⁶²

Figure 14. Effects of Early and Delayed Insulin Administration on Postmeal Glucose in Patients With Type 2 Diabetes⁶²



The rapid kinetics of the early insulin response are critical to preventing postprandial hyperglycemia; a delay of only 30 minutes has a major impact on postprandial glucose control

Neither delayed nor continuous insulin administration significantly altered the glucose response to the meal. Early insulin augmentation was associated with a more rapid postmeal decline in free fatty acid levels and a smaller rise in glucagon levels. These results support the view that a precisely timed insulin response is critical in limiting postprandial hyperglycemia. The difference between the early and delayed insulin was only 30 minutes, yet this short delay produced a large difference in control of PPG levels. This study also demonstrated that an appropriately timed early insulin response in relation to the meal is important in limiting postmeal elevations in free fatty acid and glucagon levels characteristic of type 2 diabetes.⁶²

Hepatic and Peripheral Insulin Resistance

Both hepatic and peripheral insulin resistance contribute to elevated PPG, and these actions appear to be additive to impaired insulin secretion. The importance of insulin resistance in postprandial hyperglycemia was demonstrated in 2 studies of patients with or without type 2 diabetes. In both studies, insulin secretion was inhibited with somatostatin and glucose was infused to mimic the ingestion of 50 g of glucose. In the first study, insulin also was infused in a pattern matching that in patients with diabetes after ingestion of food. In the second study, insulin was delivered to match insulin secretion in patients without diabetes. Results showed that delivery of insulin in a non-diabetic pattern to subjects with diabetes did not completely normalize glucose concentrations. Isolation of the defect in insulin action had little effect on peak glucose concentration, but it did result in a 2.5- to 4.2-fold increase in the duration of hyperglycemia. Delivery of insulin in the diabetes pattern resulted in increased peak glucose levels in subjects with or without diabetes. Both defects caused hyperglycemia by altering suppression of endogenous glucose release and disposal.⁶³

Excessive Glucagon Secretion

Insulin inhibits glucagon secretion whereby a reduction in insulin levels due to loss of early insulin response is a major factor contributing to excessive glucagon secretion in diabetes. Failure of normal suppression of glucagon secretion contributes

to the development of elevated PPG. In addition, it has been suggested that an enhanced effect of glucagon may result from increased hepatic sensitivity to this hormone. Studies have demonstrated that suppression of glucagon secretion via mechanisms other than insulin administration can decrease postprandial hyperglycemia.^{64,65}

Accelerated Gastric Emptying

Transit of nutrients through the esophagus is generally rapid, and gastric emptying is the major determinant of nutrient delivery to the small intestine. The rate of gastric emptying accounts for more than one third of the variance in peak PPG concentrations after oral glucose intake in healthy volunteers and patients with type 2 diabetes.^{64,66}

The pathophysiology and metabolic consequences of postprandial hyperglycemia are summarized in **Table 3**.⁶⁷ The initial and perhaps most important factor in the development of postprandial hyperglycemia is the loss of the early insulin response to nutrient ingestion. However, other factors also contribute to abnormally elevated PPG. Postprandial hyperglycemia has multiple deleterious effects that further compromise normal glucose homeostasis.

Table 3. Pathophysiology and Consequences of Postprandial Hyperglycemia⁶⁷

Pathogenesis	Consequences
■ Loss of early insulin response	■ Insufficient suppression of hepatic glucose output
■ Hepatic insulin resistance	■ Reduced hepatic glucose uptake
■ Muscle and fat insulin resistance	■ Inefficient peripheral glucose uptake
■ Excessive glucagon secretion	■ Abnormal tissue glucose disposal
■ Accelerated gastric emptying	■ Excessively high free fatty acid levels

Treatment of the Patient With Diabetes: Restoring Glucose Homeostasis by Matching Physiologic Insulin Secretion

Diabetes treatment involves multiple nonpharmacologic and pharmacologic interventions (**Table 4**). Patients with type 2 diabetes are likely to receive multiple antidiabetic agents as their disease progresses.⁶⁸ This section briefly discusses nonpharmacologic, oral, and incretin-based therapies as well as insulin treatment.

Table 4. Interventions Aimed at Improving Control of PPG in Patients With Type 2 Diabetes⁶⁸

Lifestyle Changes	
■ Decrease caloric intake	<i>Decrease glucose absorption</i>
■ Increase exercise	<i>Improve insulin sensitivity</i>
Non-insulin Agents	
■ Sulfonylureas	<i>Stimulate insulin secretion</i>
■ α -Glucosidase inhibitors	<i>Inhibit carbohydrate absorption</i>
■ Meglitinides	<i>Stimulate insulin secretion</i>
■ DPP-IV inhibitors	<i>Stimulate insulin secretion via incretins</i>
■ Incretin agonist	<i>Stimulate insulin secretion via GLP-1</i>
Prandial Insulin	
■ Regular human insulin	<i>Exogenous insulin replacement</i>
■ Rapid-acting insulin analogs	<i>Exogenous insulin replacement</i>
■ Insulin pump	<i>Exogenous insulin replacement</i>

Nonpharmacologic Interventions

A consensus statement by the ADA and the European Association for the Study of Diabetes (EASD) noted that a sedentary lifestyle and overeating/obesity are the most important environmental risk factors for the development of type 2 diabetes. Interventions aimed at reversing these factors have the potential to improve glycemic control.⁶⁸

Although most studies on the effects of exercise have focused on A1C, a smaller number of studies have addressed whether exercise can blunt postprandial hyperglycemia. A study of 9 young (18–25 years) and 10 middle-aged (45–65 years) sedentary women and 10 young and 10 middle-aged trained women was designed to determine whether modest exercise could reduce the rise in PPG associated with a meal that included 1 g of carbohydrate per kg of body weight. The exercise intervention was 30 minutes of light bicycle riding for 30 minutes after completion of the meal. Study results indicated that exercise decreased the postmeal rise in blood glucose in all groups of women evaluated.⁶⁹ Another study that included 12 men with type 2 diabetes showed that consuming a diet with a low glycemic index (carbohydrate items with a glycemic index <45) resulted in a significantly lower morning plasma glucose peak than a diet with a high glycemic index (carbohydrate items with a glycemic index >60).⁷⁰

The Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM) assessed the effects of a 3-year diet and exercise lifestyle intervention on glucose tolerance and insulin resistance in 147 subjects with impaired glucose tolerance. The intervention consisted of dietary recommendations based on the Dutch guidelines for a healthy diet and at least 30 minutes of exercise 5 days per week. Glucose, insulin, and free fatty acid concentrations were recorded while subjects were fasting and after an oral glucose tolerance test. Of the subjects who completed the 3-year study, the lifestyle intervention group had reduced 2-hour PPG concentrations. The reduction in postchallenge PPG was most pronounced after 1 year, but returned almost to baseline by 3 years. Nevertheless, the difference between the lifestyle intervention and control groups remained significant at 3 years.⁷¹

Oral Antidiabetic Agents

The oral antidiabetic agents used most often for control of PPG in patients with type 2 diabetes are sulfonylureas, meglitinides, and β -glucosidase inhibitors. Sulfonylureas lower plasma glucose by stimulating insulin secretion from β -cells. Administration of a sulfonylurea can produce substantial reductions in FPG and PPG in patients with type 2 diabetes who cannot achieve glycemic control with diet and exercise alone. Glipizide (5 mg) has been shown to produce a >25% reduction in the AUC for PPG from 15 minutes before to 240 minutes after a 500 kcal meal in patients with type 2 diabetes.⁷² Meglitinides (ie, repaglinide and nateglinide) also stimulate the release of insulin from pancreatic β -cells⁶⁸ and are effective in decreasing postprandial hyperglycemia in patients with type 2 diabetes. In a multicenter, randomized, double-blind study of 99 patients with type 2 diabetes who were treated with repaglinide (up to 8 mg with each meal) or received placebo for 20 weeks, repaglinide significantly decreased 2-hour PPG after a 12-oz Sustacal® meal by 104.5 mg/dL versus placebo ($P<0.05$).⁷³ While secretagogues are effective for lowering PPG, this benefit depends on the stimulation of β -cells, and the long-term efficacy of these agents in patients with depleted β -cell capacity is reduced.⁷⁴

α -Glucosidase inhibitors decrease the rate of digestion of polysaccharides in the proximal small intestine, thus lowering PPG levels.⁶⁸ Acarbose is the most commonly used agent in this class and is effective in lowering PPG and decreasing cardiovascular risk. In a 1-year, multicenter, randomized,

double-blind, placebo-controlled study, 354 patients with type 2 diabetes were treated with diet alone or diet and a sulfonylurea, metformin, or insulin.⁷⁵ The addition of acarbose (up to 200 mg with each meal) to any ongoing therapy significantly decreased PPG at 90 minutes after a standard meal versus placebo.⁷⁵ In the STOP-NIDDM trial, acarbose significantly decreased the risk of cardiovascular events in patients with impaired glucose tolerance ($P=0.02$).⁴³ A meta-analysis of 7 randomized, double-blind trials of ≥ 52 weeks duration showed that treatment of type 2 diabetes patients with acarbose significantly decreased the risk of myocardial infarction by 64% and any cardiovascular event by 35%.⁴⁵

Incretin-Based Treatment

Incretin hormones are important in augmenting the action of insulin and controlling PPG. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the 2 major human incretins. Both peptides stimulate secretion of insulin from pancreatic β -cells, but GLP-1 also suppresses glucagon secretion. Both GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase IV (DPP-IV).⁷⁶ This peptide also slows gastric emptying and decreases food consumption. These effects suggest that GLP-1 may be important in regulating postprandial glycemia. The normal GLP-1 response to a meal is reduced in patients with type 2 diabetes, and evidence shows that this loss may contribute to the disappearance of early insulin response.⁷⁶ A study of 13 patients with type 2 diabetes showed that intravenous infusion of exenatide, a synthetic peptide resembling GLP-1 and resistant to breakdown by DPP-IV, resulted in restoration of the early insulin response that was comparable to that in healthy control subjects.⁷⁷ Exenatide also has been shown to significantly lower PPG in patients with type 2 diabetes.⁷⁸

A second approach to incretin-based treatment for patients with diabetes is to inhibit DPP-IV, the enzyme that metabolizes and inactivates GLP-1 and GIP.⁷⁹ DPP-IV inhibitors are oral agents that have been used in the treatment of diabetes. Administration of sitagliptin (100 or 200 mg/d), a DPP-IV inhibitor, to 741 patients with type 2 diabetes resulted in 0.79% to 0.94% absolute decreases in A1C over 24 weeks and 48.9 to 56.3 mg/dL reductions in 2-hour PPG after a test meal.⁸⁰ These inhibitors are effective in lowering PPG, typically when used as part of a combination therapy regimen.

Incretin therapies provide moderate improvements in glycemic control similar to that achieved with metformin, sulphonylureas, or thiazolidinediones.⁸¹ The mechanism of action for incretin-based therapies complements that of insulin; however, these agents are not a substitute for insulin. According to current labeling, exenatide should be used only as adjunctive therapy to improve glycemic control in patients with type 2 diabetes taking metformin, a sulphonylurea, a thiazolidinedione, a combination of metformin and a sulphonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.⁸² Sitagliptin is indicated as an adjunct to diet and exercise in adults with type 2 diabetes.⁸³

Insulin Therapy

Oral agents commonly prescribed for patients with type 2 diabetes do not prevent the progressive loss of β -cell function during treatment.⁸⁴ The progressive nature of type 2 diabetes mandates a corresponding evolution of treatment for patients. Most patients will ultimately require insulin therapy to maintain glycemic control.⁸⁵ Current guidelines recognize that insulin is the most effective diabetes medication for the treatment of hyperglycemia. The ADA now recommends that basal insulin be added to treatment when A1C remains $\geq 7\%$ with lifestyle changes and metformin.⁶⁸ Insulin should be added to treatment regimens when a combination of oral agents does not maintain A1C at $< 7\%$.⁶⁸ Current guidelines also recommend that insulin therapy be initiated immediately in patients with severely uncontrolled diabetes with catabolism, defined as FPG > 250 mg/dL, random glucose levels consistently > 300 mg/dL, A1C $> 10\%$, or the presence of ketonuria, or in symptomatic diabetes with polyuria, polydipsia, and weight loss.⁶⁸

The goal of insulin therapy in patients with diabetes is to reach A1C targets by controlling FPG and PPG by matching, as closely as possible, the normal physiologic pattern of insulin secretion. Insulin preparations have undergone a significant evolution that has greatly enhanced the efficacy and safety of antidiabetic therapy, but current treatment options still fall short of closely mimicking normal pancreatic insulin secretion throughout the day.

Older Insulins

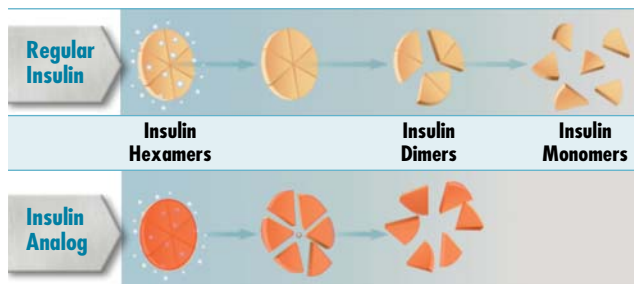
Regular human insulin has been used to control prandial glucose excursions for many years, but it must be administered 30 to 45 minutes before meal ingestion because of its slow

absorption and delayed onset of action.^{50,86} This insulin is limited by its variable absorption, which leads to inconsistency in controlling PPG. An important limitation of regular insulin is that its pharmacokinetic profile does not match the physiologic insulin secretion profile in response to a meal.⁸⁷ The requirement for injection at a long interval before meals is difficult for patients to comply with and may result in hypoglycemia if the meal is delayed or missed. In addition, the loss of the early insulin response, characteristic of patients with type 2 diabetes, is not effectively restored with regular human insulin due to its pharmacokinetic profile.⁸⁸

Intermediate-acting NPH insulin is generally used to provide a basal insulin level over the course of the day. However, its pharmacokinetic profile poorly approximates physiologic background insulin secretion. The onset of action of NPH insulin begins approximately 2 to 4 hours after subcutaneous injection; it peaks between 4 and 10 hours and is followed by a slow decline. The total duration of action for NPH insulin is 12 to 18 hours. Absorption is also variable, both within and across patients.⁸⁹

Less-than-optimal pharmacokinetic profiles for human insulin preparations are in part due to the manner in which they are manufactured. Insulin is composed of 51 amino acids in 2 peptide chains that are joined by 2 disulfide bonds. In concentrations relevant for pharmaceutical formulation, the insulin monomer assembles to insulin dimers and at neutral pH, in the presence of zinc ions, further associated to form insulin hexamers.⁹⁰ After human insulin preparations are injected subcutaneously, molecules of insulin form a depot under the skin from which insulin diffuses and is absorbed into the bloodstream. All insulin molecules self-aggregate into hexameric complexes. These complexes must dissociate into dimers and monomers before the insulin can diffuse through interstitial fluid, penetrate the capillary wall, and enter the systemic circulation.⁹¹ The self-association or aggregation of subcutaneous insulin preparations contributes to their slow and variable absorption.⁹² In addition, NPH insulin is prepared with protamine to extend its glucose-lowering effect. This ionizes the insulin molecule, which forms a complex with itself to remain in a hexameric structure at the injection site, resulting in a longer duration of action and a longer time to peak.⁹³ The time required for the aggregate of insulin molecules to separate into monomers after injection delays absorption of insulin into the circulation, producing a lower peak concentration and a longer duration of raised levels in the plasma (**Figure 15**).^{62,88,94-96}

Figure 15. Dissociation of Insulin Hexamers Into Insulin Dimers and Monomers Prior to Absorption (Top Panel) and Dissociation of an Insulin Analog (Bottom Panel)⁹⁴⁻⁹⁶



Insulin Analogs

Newer insulin analogs have partially overcome the limitations of older human insulin preparations. These newer agents include long-acting insulins, which are used to mimic physiologic basal insulin secretion, and rapid-acting insulin analogs, which are delivered at mealtime to match the physiologic spikes in insulin secretion that control PPG.

The slow absorption of subcutaneous insulins results in a slow onset of action, a delayed time to peak insulin levels, and a prolonged duration of action that does not closely mimic insulin secretion in healthy individuals without diabetes

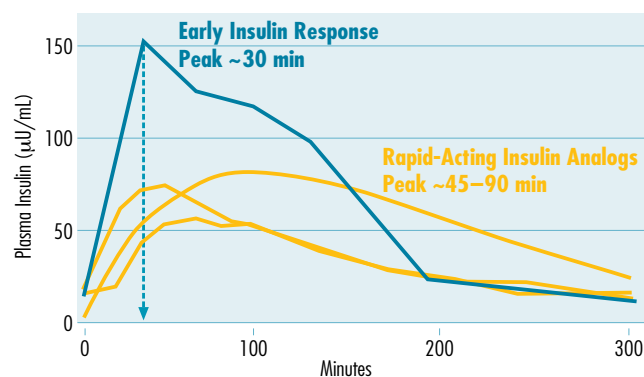
The long-acting insulin analogs, insulin glargine and insulin detemir, have improved pharmacokinetic characteristics, longer durations of action (up to 24 hours, allowing for once-daily dosing), less risk of hypoglycemia, more predictable action, and a lower propensity for weight gain than NPH insulin.⁹⁷ Insulin glargine is as effective as bedtime NPH insulin in improving glycemic control, with less hypoglycemia.⁹⁸⁻¹⁰⁰ Insulin detemir also is as effective as NPH basal insulin therapy in patients with type 2 diabetes but may require twice-daily injections in some patients.^{101,102}

Compared with regular human insulin, rapid-acting insulin analogs have a more rapid onset of action and shorter duration of action.¹⁰³ When given at mealtimes, rapid-acting insulin analogs have been shown to be more effective than regular human insulin in lowering PPG.¹⁰⁴⁻¹⁰⁶ A meta-analysis of clinical trials comparing regular human insulin with rapid-acting insulin analogs indicated that rapid-acting insulin analogs were

significantly more effective than regular human insulin in lowering PPG after breakfast (12.6 mg/dL difference between treatments) and dinner (10.8 mg/dL difference between treatments), but not after lunch.¹⁰⁷ The improved control of PPG with rapid-acting insulin analogs is most likely due to their more rapid onset of action.

However, rapid-acting insulin analogs do not replicate the normal early insulin response that is critical for suppression of hepatic glucose production (**Figure 16**).^{51,60,108-110} For example, due to the early insulin response, insulin concentration normally peaks in approximately 30 minutes.⁶⁰ In comparison, the time to peak insulin concentration following administration of rapid-acting insulin analogs is approximately 45 to 90 minutes.¹⁰⁸⁻¹¹⁰ Studies have shown that even a 30-minute delay of the insulin response can result in a significant increase in PPG excursion.^{62,111} Thus, the goal of normalizing PPG levels utilizing prandial insulin therapy that closely mimics the normal early insulin response remains an unmet need for many patients.

Figure 16. Time Versus Plasma Insulin Concentration Curves: Physiologic Pattern of Insulin Secretion Following a Meal for 3 Rapid-Acting Insulin Analogs^{60,108-110}



Duration of Action and Hypoglycemia

The risk of hypoglycemia is strongly influenced by the duration of action for an insulin used to control PPG. Several analyses have indicated that rapid-acting insulin analogs have a lower associated risk of hypoglycemia than regular human insulin. Insulin lispro, a rapid-acting insulin analog, has been shown to have a lower risk of severe and nocturnal hypoglycemia versus regular human insulin, and insulin aspart, also a rapid-acting insulin analog, has been shown to decrease the risk of severe, but not nocturnal, hypoglycemia versus regular human insulin.¹¹² Although this analysis showed that the risk of hypoglycemia is lower with rapid-acting insulin analogs than

with regular human insulin, hypoglycemia is still common in patients receiving these newer agents. In a meta-analysis of 2,576 patients with type 1 diabetes (2,327 received insulin lispro, 2,339 received regular human insulin), 3.1% of patients in the insulin lispro group experienced a total of 102 severe hypoglycemic episodes (defined as coma or hypoglycemia requiring glucagon or intravenous glucose administration) and 4.4% of patients in the regular human insulin group experienced 131 episodes during treatment.¹⁰⁴ Although insulin lispro reduced the occurrence of severe hypoglycemia in this analysis, patients taking rapid-acting insulin analogs are still at risk for this serious adverse event. These findings are consistent with those from a Cochrane meta-analysis of 8,274 patients treated in 49 randomized, controlled trials. In this meta-analysis, patients with type 1 diabetes experienced a median of 21.8 episodes of severe hypoglycemia per 100 person-years with a rapid-acting insulin analog versus a median of 46.1 episodes per 100 person-years with regular human insulin. The values for patients with type 2 diabetes were 0.3 and 1.4 per 100 person-years, respectively, for a rapid-acting insulin analog and regular human insulin.¹¹³

There is an unmet need for insulin therapy that closely mimics the early insulin response

In summary, the development of insulin analogs was a significant improvement in antidiabetic therapy. Prandial therapy with rapid-acting insulin analogs allows closer approximation of physiologic insulin secretion than regular human insulin. However, these newer preparations still do not closely mimic the normal insulin response profile seen in healthy non-diabetic individuals. Plasma levels of the rapid-acting insulin analogs start rising in less than 20 minutes and achieve peak insulin levels in 45 to 90 minutes.¹⁰⁸⁻¹¹⁰ This contrasts with the normal early insulin response, which is characterized by insulin levels beginning to rise in less than 10 minutes and peaking in approximately 30 minutes.⁵¹ In fact, the onset of action for these insulins has a delay approaching the time at which infusion of insulin had no significant effect on PPG.⁶² Rapid-acting insulin analogs are an improvement over regular human insulin since they are more rapidly cleared, which has resulted in decreasing the risk of hypoglycemia. However, all the rapid-acting insulin analogs

require approximately 6 hours for insulin levels to return to baseline.¹¹⁴ This is significantly longer than the normal early insulin response in which insulin levels return to baseline within 2 to 3 hours.

Barriers to Effective Insulin Therapy

When insulin therapy is clinically indicated, a number of factors act as barriers to initiating treatment, including patient factors (fear of needles, concern about side effects, inconvenience) and physician factors (education requirements, management of side effects; **Table 5**).¹¹⁵ Many patients with type 2 diabetes have some degree of psychological insulin resistance. This resistance may be caused by social issues (eg, the stigma of using needles), but the principal cause is the fear of having to receive or self-administer multiple insulin injections every day. Patients also have expressed a fear of inserting the needle directly into a vein.¹¹⁵ These concerns may negatively affect adherence to treatment as well as glycemic control.

Table 5. Barriers to Effective Insulin Therapy in Patients With Diabetes¹¹⁵

- Inconvenience
- Education needs
- Local reactions and pain
- Slow absorption
 - Slow onset of action
 - Delayed peak insulin level
 - Prolonged duration of action
- Hypoglycemia
- Weight gain



Weight gain is an important concern for patients initiating insulin therapy, particularly since many type 2 diabetics are already obese.¹¹⁵ Weight gain may occur because of decreased glycosuria, resulting in more glucose absorption and higher retention of calories consumed. It also may result from patients eating more to prevent or treat hypoglycemia that is associated with intensive insulin treatment. The duration of action of rapid-acting insulin analogs and regular human insulin may contribute to concern about postmeal hypoglycemia, which may lead to increased eating to treat or protect against it¹¹⁵; this is sometimes referred to as *defensive eating*.¹¹⁶

Conclusions

Strong epidemiologic data demonstrate that hyperglycemia is associated with increased risk of microvascular and macrovascular complications in patients with type 1 and type 2 diabetes. In addition, large-scale landmark studies have demonstrated that intensive glycemic control can significantly decrease the risk of these complications, particularly for primary prevention of vascular events.

A1C is determined by FPG and PPG, and observational studies and clinical trials have shown that each is an independent risk factor for diabetic vascular complications. Postprandial hyperglycemia appears to be a particularly potent risk factor for cardiovascular disease and mortality in patients with diabetes. Elevated PPG may contribute to the development of microvascular and macrovascular disease via multiple mechanisms, including formation of AGEs, stimulation of protein kinase C, initiation of growth factor-mediated vascular remodeling, and increased oxidative stress.

The normal early insulin response that peaks within minutes of a nutrient ingestion is an important determinant of PPG, acting to switch off hepatic glucose production. Delay of the early insulin response by as little as 30 minutes in human studies has resulted in significantly elevated PPG levels. The early insulin response is lost in patients with type 2 diabetes, and this contributes to the postprandial hyperglycemia characteristic of these patients. Restoration of the early phase

response with intravenous insulin in patients with diabetes results in PPG similar to that in non-diabetic individuals. Therefore, mimicking the normal early insulin response during long-term care is an appropriate strategy to achieve the goal of optimal glycemic control.

Type 2 diabetes is a progressive disease that eventually requires insulin therapy in many patients. The aim of insulin treatment is to mimic physiologic insulin secretion, but current preparations have important limitations in achieving this goal, particularly with respect to the critically important early insulin response. Because subcutaneous insulins, including rapid-acting insulin analogs, have slow absorption and kinetics, they do not closely mimic the rapid kinetics of the normal insulin response. This results in suboptimal control of postmeal glucose levels and a persistent risk of late postprandial hypoglycemia.

While many new rapid- and long-acting insulin analogs have shown benefits over regular human insulin and NPH insulin, new approaches are needed for insulin therapy with a pharmacokinetic profile that more closely approximates normal physiologic insulin secretion. Insulin therapy that lowers practical barriers to treatment (eg, fear of needles, hypoglycemia, weight gain) also has the potential to greatly improve patient willingness to undertake insulin treatment and avoid or delay the serious complications of diabetes.

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