International Forum for the Advancement of Diabetes Research and Care, April 29–30, 2011, Athens, Greece

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Abstract

The International Forum for the Advancement of Diabetes Research and Care brought together distinguished international experts in diabetes to discuss diverse trends and emerging issues in diabetes therapy and management. The plenary sessions on the first day focused on trends in insulin therapy, the role of glucagon-like peptide-1 receptor agonists in diabetes treatment, the relationship between diabetes and cardiovascular risk, and the challenges associated with the development of clinically relevant treatment guidelines. Interactive breakout sessions addressed the following topics: microvascular complications of diabetes; the need for a team approach to patient education; optimal management of Asian people with diabetes; the role of continuous glucose monitoring in assessing glucose variability; and lessons learned from biosimilar drugs. The plenary sessions on the second day covered self-monitoring of blood glucose, treatment and prevention of type 1 diabetes, and future directions for diabetes therapy. The meeting represented an excellent forum for the presentation of new research and the exchange of ideas aimed at improving outcomes for people with diabetes.

Introduction

THE 2011 INTERNATIONAL FORUM for the Advancement of Diabetes Research and Care was held in Athens, Greece, on April 29 and 30, 2011. This was the third in a series of successful meetings bringing together diabetes experts from around the world to discuss current topics and future trends in diabetes management. This year's meeting, chaired by Ele Ferrannini (University of Pisa, Pisa, Italy) and Jay Skyler (University of Miami Leonard M. Miller School of Medicine, Miami, FL), was attended by 400 people from 40 countries, with a faculty comprising 27 international experts.

The opening plenary session discussed new insights into insulin therapy, including insulin intensification strategies and early use of insulin. The second session focused on the potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in diabetes management, including preclinical data,

the GetGoal trial program, and their use in combination with basal insulins. The third plenary session commenced with a roundtable discussion of the role of guidelines in the care of people with diabetes, focusing on the challenges of making guidelines clinically relevant as well as flexible enough to individualize treatment and incorporate new therapeutic advances. The roundtable was followed by presentations on the relationship between insulin therapy and cardiovascular diseases and the influence of genetic variation on cardiovascular risk.

The first day concluded with parallel interactive breakout sessions on various topics. One session focused on microvascular complications, such as diabetic nephropathy, diabetic neuropathy, and foot ulcers, which are common and debilitating complications of diabetes and whose occurrence increases with the duration and severity of hyperglycemia.^{1,2} The growing burden of diabetes in Asia was discussed,

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including the difficulties posed by genetic susceptibility, underdiagnosis, and undertreatment. The efficacy and safety of biosimilar drugs, with particular focus on how changes in manufacturing may impact on clinical outcomes, were discussed in another session. Patient education and the role of continuous glucose monitoring (CGM) in the assessment of glucose variability were other topics covered by the breakout sessions.

The opening plenary session of the second day discussed approaches to empowering people with diabetes to take control of their disease. It started with a presentation of recent advances in self-monitoring of blood glucose (SMBG) that offer patients greater accuracy and convenience. The second talk presented clinical evidence for basal-bolus therapy as a safe and effective way to manage hyperglycemia in children and adolescents with type 1 diabetes (T1D). Preventative strategies for T1D were presented in the final talk of this session.

The Forum concluded with a look at the future of diabetes treatment. The nearly completed ORIGIN study will provide data on the impact of early insulin glargine therapy and ω -3 fatty acids on cardiovascular outcomes in type 2 diabetes (T2D). Current results from the field of β -cell replacement were presented, including in vitro generation of β cells and in vivo regeneration. The session concluded with a presentation on the Juvenile Diabetes Research Foundation Artificial Pancreas Project.

The meeting provided a comprehensive update on clinical research and treatment strategies that will help improve the lives of people with diabetes both using currently available therapies as well as with future developments in diabetes treatment.

New Insights into Fasting Blood Glucose and Glycemic Variability

Satish K. Garg

Dr. Garg discussed new insights into fasting blood glucose (FBG) and glycemic variability. The “glucose triad”—hemoglobin A1c (HbA_{1c}), FBG, and postprandial blood glucose (PPBG)—are well-established glycemic parameters that are associated with cardiovascular complications of diabetes. Guidelines for the care of people with diabetes use HbA_{1c} as the gold standard for glycemic control, with most guidelines recommending an HbA_{1c} level of <6.5% or 7.0%.

Recent data have shown that people with elevated FBG have an increased risk of death from cancer, vascular causes,

and other causes, irrespective of the diagnosis with diabetes.³ People diagnosed with diabetes and with elevated FBG face a twofold increase in the risk of coronary heart disease.³ A 5-year study comprising two arms—one arm treating fasting hyperglycemia with basal insulin (targeting FBG), the other arm treating postprandial hyperglycemia with prandial insulin injections—did not demonstrate differences in cardiovascular outcomes between study arms.⁴

Whether reductions in HbA_{1c} levels are best achieved by targeting FBG or PPBG, a subject of current debate, was addressed by Dr. Garg, who drew upon data from two studies.^{5,6} A study by Monnier et al.⁶ from 2003 analyzed diurnal SMBG profiles of 290 non-insulin-treated T2D patients at different levels of HbA_{1c} to estimate the relative contributions of FBG and PPBG to overall glycemia. Statistical analysis of SMBG data suggested that in patients with lower HbA_{1c} and relatively good glycemic control, PPBG dominated hyperglycemic exposure. However, in those with HbA_{1c} >8.4%, FBG dominated hyperglycemic exposure, and the influence of PPBG decreased. This study provided the rationale for treating PPBG rather than FBG, unless HbA_{1c} is high. A more recent meta-analysis⁵ compared the contributions of FBG and PPBG to overall hyperglycemia and its impact on HbA_{1c} using more frequent SMBG measurements, a stricter definition of hyperglycemia, and a larger sample size than in Monnier et al.⁶ and found that FBG dominated hyperglycemia across a wider range of HbA_{1c} levels than observed in the earlier analysis (Table 1). According to Dr. Garg, focusing on fasting hyperglycemia (even at lower HbA_{1c} values) may allow more patients to reach target HbA_{1c} levels.

Furthermore, when these insulin-naïve patients received insulin therapy alone for 24–28 weeks, the contribution of basal hyperglycemia to overall hyperglycemia decreased in all patients but remained higher than previously observed, regardless of their glycemic control at baseline.⁵ Numerous studies have indicated that treating to target FBG can result in significant HbA_{1c} reductions. In T2D patients with similar baseline levels of HbA_{1c}, FBG at 6–12 weeks after initiating insulin glargine predicts success in achieving HbA_{1c} ≤7.0.⁷ In T2D patients with FBG levels titrated to 5.3 mmol/L using insulin glargine, the extent of PPBG excursion was correlated with FBG ($r=0.63$, $P<0.001$), and PPBG excursions in patients with T2D and FBG <5.3 mmol/L were similar to those in controls without diabetes.⁸ These results suggest that better control of FBG (i.e., lower FBG) reduces PPBG excursions.

An expansion of the glucose triad to a glucose tetrad—HbA_{1c}, FBG, PPBG, and glycemic variability—has recently

TABLE 1. CONTRIBUTION OF BASAL AND POSTPRANDIAL HYPERGLYCEMIA TO HEMOGLOBIN A1C LEVELS AT BASELINE AND 24–28 WEEKS AFTER INITIATION OF BASAL INSULIN ACROSS GROUPS WITH VARYING METABOLIC CONTROL

	Baseline					After treatment intensification (24–28 weeks)				
	<8%	8–8.4%	8.5–8.9%	9–9.4%	≥9.5%	<6.5%	6.5–6.9%	7–7.4%	7.5–7.9%	≥8.0%
<i>n</i>	422	348	298	245	386	437	449	351	237	225
HbA _{1c} (%)	7.6	8.2	8.7	9.2	10.0	6.0	6.7	7.2	7.7	8.7
BHG (%)	76	78	79	79	80	42	41	42	43	48
PPHG (%)	24	22	21	21	20	58	59	58	57	52

Average age of the patients is 59 years, with average duration of type 2 diabetes mellitus of 9 years with fasting blood glucose of 193 mg/dL and hemoglobin A1c (HbA_{1c}) of 8.7%. Adapted from Riddle et al.⁵

BHG, basal hyperglycemia; PPHG, postprandial hyperglycemia.

been proposed.⁹ Numerous methods of measuring variability exist, and standardization of its measurement will become necessary as CGM becomes widespread. A common measure is the mean amplitude of glycemic excursions, a measure that ignores variation less than 1 SD.¹⁰ The relationship between glycemic variability and diabetes complications is not entirely clear. Glycemic variability is thought to increase oxidative stress by generating reactive oxygen species that lead to vascular damage, and there are data from *in vitro*^{11,12} and *in vivo*^{13–16} studies to support this hypothesis. However, given the small body of knowledge currently available and the lack of standardization of variability measurement, data relating to glycemic variability should be interpreted with caution. It is possible that in future we may see the use of a glucose variability index as an important tool for diabetes outcomes.

Despite the lack of standardization of measurement, growing numbers of studies are including glycemic variability as an end point, and these studies indicate basal insulins differ in their effects on variability. When measured using SD and mean amplitude of glycemic excursions, glycemic variability was observed to be significantly lower in T1D adolescents receiving insulin glargine compared with neutral protamine Hagedorn (NPH).¹⁷ A study of adults with T2D has also shown insulin glargine to reduce variability compared with NPH,¹⁸ whereas levels of glycemic variability in insulin-naïve T2D adults receiving glargine or detemir appeared to be similar.¹⁹

Dr. Garg concluded that current evidence supports FBG as a target for glycemic control and that good control of FBG has beneficial effects on PPBG. Expanding the glucose triad to the tetrad of HbA_{1c}, FBG, PPBG, and a standardized measure of glycemic variability will be a potentially useful step, as the clinical implications of variability emerge. Currently, the primary focus for treatment of people with diabetes should be to keep HbA_{1c} < 7.0%, by targeting FBG levels.

Optimal Use of Insulin Therapy in People with Diabetes

Geremia B. Bolli and David R. Owens

Dr. Bolli reviewed the rationale behind initiating insulin therapy with basal insulin and presented new data on the pharmacokinetic and pharmacodynamic properties of insulin analogs. Basal insulin activity is essential for suppression of hepatic glucose production and maintenance of normoglycemia. Although continuous subcutaneous insulin infusion via a pump is the gold standard in producing steady insulin levels, continuous subcutaneous insulin infusion is best suited to T1D and not the early stages of T2D. American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) guidelines recommend basal insulin as a well-validated tier 1 therapy in patients with T2D for whom lifestyle measures and metformin fail to achieve glycemic control (HbA_{1c} ≤ 7%).²⁰ Premixed insulins are not recommended for insulin initiation.²⁰

NPH often falls short of providing an appropriate basal insulin because of variable absorption, undesirable peaks in hypoglycemia, and insufficient duration of action, particularly in T1D (including peaks and troughs in glucose excursions).²¹ The long-acting basal insulin analog insulin glargine closely mimics physiological basal insulin release and was introduced into clinical practice in 2000. It is administered

once daily, has a long duration of action (24 h), and does not produce a pronounced peak in plasma insulin.^{22–25} Randomized controlled trials and meta-analyses have shown that insulin glargine is as effective as NPH but is associated with significantly fewer hypoglycemic episodes.^{26,27} Insulin detemir, a long-acting insulin analog introduced in 2006, also exhibits a more physiological activity profile than NPH²⁸ and has been shown to significantly reduce hypoglycemia rates compared with NPH.^{29,30}

Pharmacodynamic studies in patients with T1D showed that glargine and detemir have similar effects on glucose metabolism for the first 12 h, followed by a progressive decline in activity and a significantly lower per-unit activity with detemir of approximately 30%.²³ In a trial of 443 individuals with T1D comparing glargine and detemir as the basal component of a basal-bolus regimen, those receiving detemir (66% twice daily) required a 21–42% higher dose compared with those receiving once-daily glargine, despite both groups achieving similar glycemic outcomes.³¹ In T2D, comparative clinical studies of insulin glargine and insulin detemir in patients with T2D have reported clinically significant and similar improvements in glycemic control and similarly low rates of hypoglycemia but with significantly lower dose requirement in those receiving insulin glargine.^{19,32}

A recently published three-way, crossover study directly compared NPH, detemir, and glargine in T2D.³³ The glucose infusion rate area under the curve (for 0–32 h) was significantly greater for insulin glargine compared with NPH or detemir (Fig. 1), and glargine suppressed endogenous glucose production significantly more than detemir and similarly to NPH.³³ Comparisons of glucose infusion rate and body mass index (BMI) among patients using detemir, NPH, or glargine indicated that in patients with a BMI > 29 kg/m² glargine had a higher activity³⁴ and that daily dose and BMI are more strongly correlated in patients using detemir compared with glargine.³⁵

Dr. Owens presented the clinical evidence supporting a stepwise transition from basal insulin to basal-plus and basal-bolus regimens. The use of basal insulin as an appropriate way to initiate insulin therapy in patients with T2D is supported by the 4T Study.³⁶ In this study, 708 patients with inadequate glycemic control on oral antidiabetes drugs (OADs) were randomized to receive basal, biphasic, or prandial insulin in the first year, and if glycemic control remained inadequate, therapy was intensified in years 2 and 3 by the addition of prandial insulin to the initial basal and biphasic regimens or the addition of basal insulin to the initial prandial insulin.³⁶ A significantly higher proportion of patients in the basal- and prandial-initiating groups achieved an HbA_{1c} ≤ 7.0% at 3 years.³⁶ Additionally, initiating therapy with basal insulin resulted in reduced weight gain and fewer hypoglycemic episodes.

The progressive nature of T2D means that many patients need to add bolus insulin to reduce postprandial glycemic excursions. Even among T2D patients in whom metabolic control is still apparently good (HbA_{1c} < 7%), significant PPBG excursions can occur, and hence the need for additional bolus insulin to maintain good glycemic control.³⁷ Insulin glulisine is well suited as a bolus insulin because of its fast onset and short duration of action.³⁸

Dr. Owens addressed the question of whether a single bolus is more effective at a particular mealtime using data

FIG. 1. Plasma glucose after a subcutaneous injection of neutral protamine Hagedorn (NPH) (gray circles), detemir (open circles), or glargine (solid circles) insulin in type 2 diabetes patients ($n=18$). s.c., subcutaneous. Adapted from Lucidi et al.³³

from the OPAL study; this study included 393 T2D patients inadequately controlled with basal glargine and OADs who were randomized to receive a single insulin bolus after breakfast or the “main” meal as defined by the highest 2-h PPBG measurement.³⁹ A single bolus of glulisine was effective in reducing HbA_{1c} levels irrespective of when it was given. The HbA_{1c} reduction from baseline to end point was significant in both the breakfast arm and the main meal arm, but the difference between the end point HbA_{1c} values of the two arms was not significant.³⁹ In the 1-2-3 Study, patients inadequately controlled on OADs underwent a 14-week run-in period with insulin glargine, and those patients with HbA_{1c} >7.0% at the end of the run-in were randomized to insulin glulisine once, twice, or three times daily.⁴⁰ HbA_{1c} reductions with once- and twice-daily insulin glulisine were non-inferior to those with glulisine three times daily, and a nonsignificant trend for lower rates of hypoglycemia was observed in the once- and twice-daily groups.⁴⁰

Basal glargine plus bolus glulisine at mealtimes was compared with twice-daily premixed insulin in T2D patients taking OADs in the GINGER study;⁴¹ patients receiving the basal glargine and prandial glulisine regimen showed superior reductions in HbA_{1c} compared with those receiving premixed insulin, and a higher percentage of the basal-bolus patients achieved HbA_{1c} ≤7.0% (Fig. 2).

Clinical evidence confirms that basal and prandial insulin analogs are better for insulin replacement and are an improvement over NPH insulin and regular human insulin in terms of duration of action and safety. Further research on the pharmacokinetic and pharmacodynamic properties of different insulin analogs will better define the effects of these analogs on physiological parameters other than glycemia. There is strong evidence to support initiation of insulin therapy

using basal insulin, followed by a stepwise transition to basal-plus and then basal-bolus where necessary.

Does Early Use of Insulin Reduce Complications of Diabetes?

John L. Leahy

Dr. Leahy discussed the rationale for early insulin use and clinical evidence in support of early intensive therapy.

Cardiovascular disease is the major clinical complication in people with T2D, responsible for 50–80% of diabetes-related mortality.⁴² Dr. Leahy presented data from the United Kingdom Prospective Diabetes Study (UKPDS) showing that intensive glucose therapy in patients with newly diagnosed T2D was associated with a reduced risk of clinically evident microvascular complications (neuropathy, nephropathy, and retinopathy) and a nonsignificant reduction of 16% in the relative risk of myocardial infarction.⁴³ The inconclusive result seen for the risk of myocardial infarction led to speculation that an HbA_{1c} target even lower than the average 7% achieved in the trial may be desirable. Subsequent reanalysis of the study findings confirmed the previous results and demonstrated that reducing HbA_{1c} by as little as 1% could lead to a 37% decrease in microvascular complications.⁴³ It is important that the UKPDS data also showed a long-term “legacy” effect of early intensive treatment long after the end of the randomized treatment intervention phase of the study.⁴⁴ Although in-between group differences in HbA_{1c} levels were lost within the first year of stopping the trial, significant relative risk reductions in both microvascular and macrovascular complications persisted at 10 years in the sulfonylurea–insulin group (Table 2). More recent studies of persons with longstanding T2D at high cardiovascular risk—

FIG. 2. Glycemic outcomes of the GINGER study. (A) Hemoglobin A_{1c} (HbA_{1c}) reductions seen in the GINGER study using premix insulin, twice daily, 91 U/day (solid line), or a basal-bolus regimen, insulins glargine + glulisine, 98 U/day (dashed line). A larger fall in HbA_{1c} is seen using basal-bolus compared with premix (−1.31% vs. −0.80%, $P=0.0001$). (B) Percentage of patients achieving HbA_{1c} <7.0% using premix insulin or a glulisine + glargine basal-bolus regimen. More reached HbA_{1c} <7% using glulisine + glargine compared with premixed insulin (46.6% vs. 27.9%, $P=0.0004$). HbA_{1c} data are unadjusted mean $\pm$ SE values. Adapted from Fritsche et al.⁴¹

the prospective ACCORD,⁴⁵ ADVANCE,⁴⁶ and VADT⁴⁷ trials—were less conclusive for a protective role of intensive blood glucose control on cardiovascular risk than the UKPDS data in the overall study populations. However significant reductions in cardiovascular complications were observed, when “early” subgroups—HbA_{1c} <8%,⁴⁵ no history of macrovascular disease,⁴⁶ and shorter duration of diabetes⁴⁷—were analyzed. Collectively these results imply a cardiovascular protective effect of intensive blood glucose control when used early. However, whether the observed effects are

treatment-specific or related to tight blood glucose control remains a matter of debate. For instance, a retrospective U.S. database analysis at a mean follow-up of 2 years suggested a reduced risk of acute myocardial infarction in patients treated with insulin glargine compared with NPH.⁴⁸

Early intervention with insulin therapy may also have a protective effect on β -cell function.^{49–52} In a Chinese trial, 382 patients with new-onset T2D were randomly assigned to intensive therapy with an insulin pump, a multiple daily injection insulin program (NPH and insulin), or OADs for initial rapid correction of hyperglycemia.⁵² Treatment was stopped after normoglycemia was maintained for 2 weeks, and patients were followed up on diet and exercise alone. One year after the initial therapy, approximately 50% of the patients in the insulin groups were still without therapy and had HbA_{1c} levels within the normal range,⁵² highlighting the potential long-lasting impact of early intensive insulin treatment. Measurements of β -cell function at trial end and 1 year later showed higher β -cell activity in the insulin therapy remission groups than the OAD remission group. As the remission rate on OADs was much lower, it suggests that the observed effect may be insulin specific.

Addition of basal insulin to initial concurrent lifestyle measures and metformin is recommended by the ADA/EASD consensus guidelines if HbA_{1c} target levels (<7.0%) are not achieved.²⁰ However, insulin is often not initiated until many years of poor glycemic control have elapsed and HbA_{1c} levels are high,^{53,54} despite clinical data demonstrating the importance of early intervention. A large database analysis of patients treated with insulin glargine indicated baseline HbA_{1c} correlates with the proportion of patients reaching HbA_{1c} <7%.⁵⁵ Approximately 75% of patients with a baseline HbA_{1c} of <8.0% reached that target, compared with only 34%

TABLE 2. LEGACY EFFECT OF EARLY INTENSIVE INTERVENTION ON DIABETES COMPLICATIONS AFTER POST-TRIAL FOLLOW-UP OF 8.5 YEARS (MEDIAN) IN THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY

Aggregate end point	1997 ^a	2007
Any diabetes-related end point		
RRR	12%	9%
P	0.029	0.040
Microvascular disease		
RRR	25%	24%
P	0.0099	0.001
Myocardial infarction		
RRR	16%	15%
P	0.052	0.014
All-cause mortality		
RRR	6%	13%
P	0.44	0.007

Adapted from Holman et al.⁴⁴

^aEnd of randomized intervention with sulfonylureas/insulin versus conventional treatment.

P, log rank; RRR, relative risk reduction.

of patients with a baseline HbA_{1c} of $\geq 9.5\%$. Hypoglycemia was similar for all levels of baseline HbA_{1c}, with the highest rate of hypoglycemia requiring assistance in patients with a baseline HbA_{1c} of 8.5–8.9%.⁵⁵

Further information on the effects of early insulin treatment is expected from the ORIGIN trial, the results of which are expected in 2012; the ORIGIN trial is investigating the effect of insulin glargine and ω -3 fatty acids on cardiovascular complications in prediabetes and early T2D (HbA_{1c} of approximately 6.5%).⁵⁶ In this large study, 12,612 patients were randomized to receive either insulin glargine and metformin or a standard step therapy. Each of these groups was then further subdivided to receive either placebo or ω -3 fatty acids. The primary outcomes investigated include cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The incidence of all-cause mortality and microvascular events will be secondary outcome measures of the trial.

Reducing the morbidity and mortality of the cardiovascular complications of diabetes is central to improving the care of people with diabetes. As the greatest benefits of glycemic control on the prevention of cardiovascular complications are seen when glycemic control is established early in the disease, early use of insulin can play an important role.

Lixisenatide: The GetGoal Program and Recent Results

Matthew C. Riddle

Lixisenatide is a new GLP-1 receptor agonist in late-stage clinical development. Dr. Riddle provided an overview of properties of lixisenatide and clinical data obtained to date, focusing on the Phase III GetGoal program.

In preclinical studies, lixisenatide was shown to stimulate insulin secretion in a glucose-dependent manner, delay gastric emptying, and prevent β -cell apoptosis in cell culture.^{57,58} In human studies, once-daily lixisenatide demonstrated a strong, dose-dependent effect on postprandial glucose levels, particularly after breakfast.⁵⁹ A 13-week, double-blind, placebo-controlled, Phase IIb dose-ranging study of lixisenatide was conducted in 542 patients with T2D not controlled with metformin.⁶⁰ The efficacy and safety of 5, 10, 20, or 30 μ g of lixisenatide given once or twice daily were assessed. At the end of the trial, significant dose-dependent reductions in HbA_{1c} and FBG were seen compared with placebo; significant reductions were also seen in 2-h PPBG and in body weight.⁶⁰ Lixisenatide was generally well tolerated, with the most frequent adverse effect being nausea. Based on the efficacy and safety data from this study, a 20 μ g, once-daily dose was selected for further clinical evaluation.

The GetGoal program is an extensive Phase III clinical trial program investigating lixisenatide and comprises 10 clinical trials with over 4,300 participants in 49 countries (Fig. 3). Lixisenatide is being evaluated as monotherapy, as an add-on to metformin or sulfonylureas, and as an add-on to basal insulin. To date, preliminary results have been reported from the GetGoal Mono,⁶¹ GetGoal-L Asia,⁶² and GetGoal-X⁶³ studies.

GetGoal-Mono evaluated lixisenatide in 361 treatment-naïve T2D patients over a 12-week period, comparing one- and two-step titration regimens of a once-daily 20 μ g dose.⁶¹ Patient age, BMI, and duration of diabetes were similar between groups. Both one- and two-step regimens produced similar reductions in HbA_{1c} from baseline compared with

placebo and similar changes in FBG from baseline. Lixisenatide had a pronounced effect on PPBG, with significant reductions in 2-h PPBG compared with placebo. The safety and tolerability profile observed was good, and weight loss was similar in all groups. GetGoal-L-Asia evaluated the efficacy and safety of lixisenatide on top of basal insulin (with or without sulfonylureas) in 311 T2D patients in Asia.⁶² Compared with placebo, patients receiving lixisenatide had a change in HbA_{1c} of -0.88% during a 24-week trial. There were no specific safety signals arising from the trial. The GetGoal-X trial is a randomized, open-label, active-controlled study that has compared the safety and efficacy of once-daily lixisenatide with twice-daily exenatide in 639 patients over a 24-week treatment period. Lixisenatide demonstrated comparable effects to exenatide in reducing HbA_{1c}, FBG, and body weight, and significantly fewer hypoglycemic events were observed in the lixisenatide group compared with the exenatide group.⁶³

In addition to the GetGoal program, the effects of lixisenatide on cardiovascular outcomes are being evaluated in 6,000 T2D patients in the 44-month ELIXA trial. When complete, in October 2013, ELIXA will add valuable new data on the long-term safety of lixisenatide as well as effects on cardiovascular outcomes such as stroke, angina, and myocardial infarction (<http://clinicaltrials.gov/ct2/show/NCT01147250>).

GLP-1 agonists and basal insulin may be suitable as combination therapy because of their common features, such as simple dosing regimens and low risks of hypoglycemia, and potential complementary effects on PPBG and FBG, respectively. Such a combination therapy was recently evaluated in a 4-week trial of 48 T2D patients assigned to groups given placebo, exenatide, or sitagliptin, in combination with insulin glargine and metformin; the 6-h PPBG excursions, as measured by blood glucose area under the curve, were significantly lower in the exenatide and sitagliptin groups compared with the placebo group.⁶⁴ Exenatide in combination with insulin glargine was also evaluated recently by Buse et al.⁶⁵ in T2D patients in a placebo-controlled trial; in the exenatide group, the decrease in HbA_{1c} levels was significantly greater than in the placebo group, and weight decreased by 1.8 kg in the exenatide group compared with an increase of 1.0 kg in the placebo group. The ability of lixisenatide–glargine combination therapy to further improve glycemic control is being evaluated in the ongoing Insulin Glargine Optimization Study (<http://clinicaltrials.gov/ct2/show/NCT00975286>).

Lixisenatide has beneficial effects on glycemia, especially PPBG, with a good safety profile and is effective when given as a single daily dose. Furthermore, lixisenatide has the potential to further improve glycemic control when used in combination with basal insulin. Clinical studies to date indicate lixisenatide will be a useful treatment option for people with T2D. The GetGoal program will provide a wealth of data that will contribute to a better understanding of the safety, efficacy, and cost-effectiveness of GLP-1 agonists.

Patient Education and Integrated Care: Addressing the Major Challenges

Larry C. Deeb, Phil Southerland, and Ellie S. Strock

The difficulties of providing integrated diabetes care and education and the most effective ways achieving this were discussed by Dr. Deeb, Ms. Strock, and Mr. Southerland.

FIG. 3. The Phase III GetGoal program: approximate timelines of 10 studies supporting lixisenatide registration. SU, sulfonylurea.

Diabetes is influenced by a patient's choices in diet, exercise, and other lifestyle factors, and effective patient education plays a crucial role in producing successful treatment outcomes. Individuals with diabetes may need to draw upon expertise from dietitians, medical specialists, and exercise specialists as well as general physicians. Specialized diabetes educators can help integrate the skills and advice of a diverse care team into a patient-centric approach to care.

An integrated approach to diabetes care and education has been reported in a Latino-American population with T2D in San Diego County, CA.⁶⁶ This program consisted of a nurse case-management approach led by a registered nurse/certified diabetes educator with assistance from dietitians and diabetes patients trained as peer-educators. Nurses in this program worked closely with primary physicians and made recommendations for follow-up laboratory work and changes in medication to primary physicians. Staged Diabetes Management (SDM; International Diabetes Center, Minneapolis, MN) was used to provide consistent diabetes management. This integrated approach resulted in average HbA_{1c} reduction of -3.5% (from 11.8% to 8.3%) in the intervention group, compared with a reduction of -1.1% (from 11.5% to 10.4%) in the control group (Fig. 4).⁶⁶ Ms. Strock concluded that education that is more tightly integrated with the primary physician achieves better outcomes for patients.

As the global healthcare expenditure on diabetes rises,⁶⁷ it is crucial that education programs are cost effective. New approaches such as group education, peer education, and new technologies can help keep education costs under control and improve the reach of education. Education delivered to a small group can be as effective as individual education in achieving reductions in HbA_{1c}.⁶⁸ With appropriate training, lay-educators may be as effective in training individuals as

specialized healthcare professionals.⁶⁹ This may be especially so in minority groups where peer-educators may be able to avoid language barriers and receive more direct answers from patients who may be embarrassed about their lack of education or healthcare habits. Recent studies indicate internet-based blood glucose management programs can improve self-monitoring behavior and have beneficial effects on HbA_{1c} levels.^{70,71} As blood glucose meters become integrated with mobile internet devices, such programs will become more convenient and reach more patients.

Further benefits to patients and reductions in costs can be achieved with the adoption of appropriate care guidelines in clinical practice. Specialized care teams offer significant benefits to patients, but general practitioners are the primary providers of care for the majority of people with diabetes.^{72,73} Dr. Deeb discussed the topic of SDM, a set of tools developed by the International Diabetes Center to translate new research findings into clinical practice for primary care physicians.⁷⁴ SDM comprises a set of assessments, audits, and customizable guidelines that include all healthcare and health-education team members. Implementation of SDM can reduce healthcare costs and increase quality of care,⁷⁵ and implementation of integrated care based on SDM principles can result in improvements in glycemic control in people with diabetes.⁷⁶

Mr. Southerland, diagnosed as an infant with T1D, shared with the audience his experiences of integrated diabetes management. A former professional cyclist, Phil is founder and CEO of Team Type 1, a professional cycling team that works to promote diabetes education. He discussed the challenges and stresses he and his family faced as a child with diabetes and the difficulty of good self-care during the transition to adulthood. Empowerment tools, such as glucose monitoring, self-titration of insulin, and education on how to

FIG. 4. Outcomes of integrated diabetes education and care: a comparison of hemoglobin A1c (HbA_{1c}) levels at baseline (solid columns) and 1 year after initiation of a peer education/empowerment program (open columns) in control and intervention groups ($n = 153$). * $P < 0.0001$ intervention versus control. Adapted from Philis-Tsimikas et al.⁶⁶

best manage blood glucose, are essential to giving patients a sense of control over their diabetes.

Appropriate education in self-care will be essential to meet the challenge posed by diabetes without overwhelming healthcare resources. Certified educators and new models of education, such as patient-educators and internet-delivered care, can contribute significantly to reducing this burden. Identifying the most effective mix of formal, peer, and electronically delivered training for different population groups requiring help should be a priority for studies in this area. On a broader scale, adopting systematic guidelines for the primary care of people with diabetes can also improve patient outcomes.

Glucose Variability in T1D, T2D, and Diabetes in Pregnancy

Roger S. Mazze

An underlying principle in the treatment of T1D and T2D has been to mimic normal glucose metabolism in order to impart on the person with diabetes the same low risk of microvascular and cardiovascular disease as an individual without diabetes. This principle has also been advanced in pregnancies complicated by pre-gestational and gestational diabetes in order to reduce the occurrence of fetal malformations, miscarriage, and other adverse perinatal outcomes. Recently, the principle has taken on greater significance with the discovery that early achievement of near-normal glycemic control triggers a metabolic memory, which may lessen the risk of long-term complications despite subsequent deterioration in glycemic control.

Although the pathways from hyperglycemia to complications are manifold and as yet not completely understood, some conclusions have already been reached. First, any period of hyperglycemia appears to increase the risk of complications independent of type of diabetes. Second, there seems to be a linear relationship between the level of hyperglycemia and risk. Third, improved glycemic control following long-term hyperglycemia may not lessen risk. Fourth, hyperglycemia compounded by oscillations, especially into the hypoglycemic range, worsens the risk of long-term complications and may induce acute complications such as cardiac events.⁷⁷ The pathway from glucose variability and hyperglycemia to cellular damage and consequential microvascular and macrovascular disease includes the hyperproduction of reactive

oxygen species, which damage mitochondrial and genomic DNA. Under laboratory conditions, for individuals with normal glucose metabolism, high concentrations of glucose produce "significant endothelial dysfunction."⁷⁸ When these high levels of glucose are subjected to oscillations, such as during postprandial periods, the dysfunction worsens.^{78,79} This condition is exaggerated in individuals with diabetes. The notion that both individuals with normal and abnormal glucose metabolism are at risk for irreparable cellular damage leading to vascular complications suggests that avoiding glucose oscillations is a protective mechanism. Measuring glucose variability is a challenge, as it requires a means of characterizing diurnal glucose patterns under conditions of normal living. Until the advent of CGM this was not feasible. CGM provides comprehensive glucose profiles by capturing glucose values otherwise unmeasured.⁸⁰⁻⁸² With CGM it has become possible to, with minimum interference, accurately and reliably capture the manifold alterations in glucose control experienced by both those individuals with diabetes and those with normal glucose tolerance.^{83,84}

Over the past 5 years, CGM has been used in more than 700 subjects at varying levels of glucose metabolism to produce ambulatory glucose profiles (AGPs) in order to quantitatively and graphically depict diurnal patterns, glucose exposure, variability, and stability.⁸¹ AGP analysis is a common reporting system that aggregates and analyzes data independent of the device manufacturer's proprietary and distinctive software. All data are aggregated as if they occur on a single or modal day and are represented by five continuous smoothed curves representing the 10th, 25th, 50th, 75th, and 90th frequency percentile (Fig. 5). The data are displayed along with measures of glucose exposure (area under the median curve), variability (interquartile range), and stability (hourly change in the median curve). Additionally, the AGP report contains graphic displays of daily oscillations.

As displayed in Figure 5, AGP analysis enables rapid detection of glucose variability in subjects with normal glucose metabolism (Fig. 5a) and those with diabetes (Fig. 5b). Note the overall glucose profile of the individual in Figure 5a shows almost no variability following meals. Closer analysis of individual days reveals periodic postprandial excursions averaging <35 mg/dL from the preprandial levels. These excursions are typical of individuals without diabetes and may serve as a reference. The daily oscillations in Figure 5b, for an individual with T2D (HbA_{1c} 6.7%; mean glucose, 135 mg/dL),

FIG. 5. Ambulatory glucose profiles obtained via continuous glucose monitoring of (a) an individual without diabetes with normal glucose metabolism and (b) an individual with type 2 diabetes and abnormal glucose metabolism. AUC, area under the curve; BMI, body mass index; CGM, continuous glucose monitoring; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; Ht, height; IQR, interquartile range; Max, maximum; Min, minimum; SBP, systolic blood pressure; Wt, weight. [Source of data: International Diabetes Center, St. Louis Park, Minnesota]

reveals pre- to postprandial excursions reaching 150 mg/dL. Even the SD (40 mg/dL) does not reflect these oscillations. Furthermore, some of these excursions occurred overnight, at times when routine monitoring (SMBG) does not occur.

There is mounting evidence that glucose variability as expressed in daily oscillations has a deleterious effect on the cascade of physiologic events that result in acute and chronic vascular disease. Among people with diabetes, the detection of these oscillations may identify a high-risk group.^{85,86} Achieving metabolic control early to abate glucose oscillations may minimize risk of imminent and long-term complications in individuals with diabetes. The same phenomenon—glycemic variability—occurs in individuals without diabetes during periods of acute cardiovascular events.⁸⁷ Consequently, using CGM in these individuals to accurately capture daily oscillations may help select interventions that rapidly restore their normal diurnal glucose patterns. Identifying and anticipating the extreme fluctuations can serve to eliminate or reduce the exacerbation of pathways contributing to the pathogenesis of vascular disease.

Acknowledgments

Michael Bancks contributed to the preparation of R.S.M.'s section of this report, specifically, review of the literature, assembly of references, and copyediting. Medical writing support was provided by nspm Ltd., Meggen, Switzerland, funded by Sanofi, Paris, France.

Author Disclosure Statement

G.B.B. has received grants, honoraria, or consulting fees from Bristol Mayer Squibb, Eli Lilly, Lifescan, Mannkind, Menarini, Novartis, Roche, and Sanofi. L.C.D. has received research support from Abbott, Bayer, the National Institutes of Health, Eli Lilly, Novo Nordisk, and Pfizer and is on a Speakers Bureau for Novo Nordisk and Sanofi. S.K.G. has received honoraria for giving lectures and grants through the University of Colorado from Abbott, Animas, Daiichi Sankyo, DexCom, Eli Lilly, Johnson & Johnson, Medtronic Minimed, Merck, Novo Nordisk, and Sanofi. J.L.L. has received consulting fees from Merck, Novo Nordisk, Sanofi, and Takeda and a research grant from Takeda. R.S.M. has received research funding from Abbott, Roche, and Sanofi. D.R.O. has consulted for Roche and Sanofi, been a speaker for Boehringer Ingelheim, Novo Nordisk, Roche, and Sanofi, and received grant and research support from Roche and Sanofi. M.C.R. has received research grants from Amylin, GSK, Lilly, and Sanofi, honoraria for consulting from Amylin, Lilly, Novo Nordisk, Roche and Sanofi, and honoraria for speaking from Lilly and Sanofi. P.S. has been a speaker for Insulet and Sanofi. E.S.S. has received research support from Abbott, Roche, and Sanofi.

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