MEETING REPORT

6th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG) Applications and Beyond, April 25–27, 2013, Riga, Latvia

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Abstract

International experts in the fields of diabetes, diabetes technology, endocrinology, and pediatrics gathered for the 6th Annual Symposium on Self-Monitoring of Blood Glucose (SMBG) Applications and beyond. The aim of this meeting was to continue setting up a global network of experts in this field and provide an international platform for exchange of ideas to improve life for people with diabetes. The 2013 meeting comprised a comprehensive scientific program, parallel interactive workshops, and two keynote lectures. All these discussions were intended to help identify gaps and areas where further scientific work and clinical studies are warranted.

Opening Lecture: News from the World of Diabetes

Satish Garg, University of Colorado Denver, Aurora, Colorado

Drugs can't do it alone, we need technology too

SATISH GARG, IN HIS OPENING lecture, gave insights into the status of diabetes care in general, described the direction of the ongoing diabetes research, and unveiled exciting technological advances coming our way in the near future. He argued that diabetes technology has a major contribution to make on the quality of life and the day-to-day interaction between patient and disease. He put forward a poignant question, saying that we are almost spoiled for choice by the number of antidiabetes agents currently available to treat diabetes, but has that changed patient outcome?

Garg advocated that drugs cannot do it alone and that there is a clear gap in the management of diabetes that may be filled in by diabetes-related technologies.

Diabetes: uncontrollable cost

Garg presented recently published data that show the cost of diabetes alone amounts to a staggering \$245 billion per year in the United States.¹ This figure is expected to rise in the future. Almost one-third of people with diabetes belong to the elderly age group (above 65 years of age), meaning that most individuals have been systematically excluded from research trials and clinical studies. Garg made a timely and passionate plea that *elderly people with diabetes must not be left out of the diabetes research agenda*.

A closer examination of the cost of diabetes expenditure reveals that 80% of the money is used to pay for services and late complications. Eight percent of the total expenditure is used for diabetes technology. Garg suggested that people with diabetes should be cared for from the outset to reduce the expense incurred due to late complications.

Glycated hemoglobin and hypoglycemia as measures of healthcare outcome

Recent clinical data of 25,000 people with type 1 diabetes attending 67 leading diabetes centers across the United States were presented by Garg. The T1D Exchange Study² is an observational study that showed several interesting findings. First, despite all existing efforts, the pursuit of the target glycated hemoglobin (HbA1c) level remains elusive for many people with diabetes across the United States. Second, the incidence of hypoglycemia remains a major concern for many people with diabetes, especially the elderly. Another and unexpected finding of the T1D Exchange Study was the observation that intensified metabolic control was not accompanied by higher rates of hypoglycemia in the patients studied. Garg cautioned that the study in question was cross-sectional in nature and that consequently data should not be interpreted at mere face value.

Regarding people with type 2 diabetes, an optimal HbA1c target level has been the focus of a recently released guidelines statement. There is not one target level of HbA1c that fits all, and neither overaggressive nor loose metabolic control was ideal for the people with type 2 diabetes. Garg identified recent data³ suggesting HbA1c levels of around 7.6% were

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associated with less adverse cardiovascular outcomes and may therefore appeal as an appropriate target level.

Imperfect insulins

Insulin therapy represents the cornerstone of current and future diabetes therapy. The industry has been working constantly on the development of new insulins that are safe, effective, and relatively physiological.

Degludec is a new ultra-long-acting basal insulin recently released into the market in Europe and Japan. Degludec has been used in trials for people with either type 1 or type 2 diabetes. It has improved metabolic control and induces fewer nocturnal episodes compared with standard basal insulin therapy.^{4,5} In the United States, however, degludec approval has been delayed by the Food and Drug Administration pending completion of cardiovascular outcome studies.

Garg emphasized that “rapid-acting prandial insulins” in reality are not rapid enough for effective control of postprandial glucose levels. In numerous continuous glucose monitoring (CGM) studies, rapid-acting insulin analogs need to be injected at least 20–30 min before mealtime for the insulin action to coincide with the expected glucose excursion. There have been several innovative ideas and experiments conducted with varying degrees of success (e.g., vitamin E as a vasodilator). He described exciting work on a type of hexameric insulin. It is manufactured with a built-in glucose sensor that can spontaneously estimate the prevailing glucose concentration and eliminates the need for prandial insulin injections. We should expect new data in this area over the coming year or two, Garg offered.

Self-monitoring of blood glucose, CGM, mobile technology: the way forward to the future

Clinical studies suggest that the quality of metabolic control is dependent on the frequency of self-monitoring of blood glucose (SMBG).⁶ Garg stated that the change in HbA1c can drop by as much as 2% between those who check their blood glucose (BG) levels diligently (eight times a day) versus those who do not. Garg revealed the average time a physician spends with an individual patient with diabetes is estimated to be only 21 min per year! Given the thousands of hours patients are left alone, abandoned to their own devices, there is a clear need to embrace and implement mobile technology. Garg unveiled a new trial called the Remote-T1D Study, which addresses the use of mobile technology as a method to help bridge the gap between patient and doctor.⁷

CGM sensors have the potential to improve metabolic control and reduce the incidence of hypoglycemia.⁸ Garg wondered, despite the fact that CGM is widely available and largely covered by insurance companies, why it is limited to only 10% of people with type 1 diabetes. Factors such as general cost of CGM and the need for proper education may be hindering the wider implementation of CGM use in clinical practice. Garg called for CGM information to be presented in a practical form and tailored to meet the needs of people with diabetes. Garg suggested that many CGM trials undertaken in the past have consistently excluded patients troubled with severe hypoglycemia. Garg argued that the value of CGM application is not confined to people with type 1 diabetes. Recent work by Vigersky et al.⁹ demonstrated a significant and relatively lasting improvement in HbA1c despite limited

and intermittent use of CGM sensors in people with type 2 diabetes.

From standard insulin pump to closing the loop completely

Compared with treatment using multiple daily injections (MDI) regimens, insulin pump therapy has been associated with a consistent improvement in HbA1c of approximately 0.5%.¹⁰ Garg suggested that in about 12% of people with diabetes starting pump therapy, no improvements are seen. Contributing factors need to be identified and studied. Reduction in the rate of hypoglycemia with pump therapy has not always been easy to prove in individual clinical trials, but a recent meta-analysis has clearly shown its benefits.¹¹ Use of an insulin pump seems to be more rewarding in the elderly and those with a longer duration of diabetes, Garg noted.

The STAR-3 study testing sensor-augmented pump therapy demonstrated a clear reduction in HbA1c compared with MDI therapy.¹² The In-Clinic ASPIRE study, where hypoglycemia was deliberately induced by exercise, showed that duration and severity of hypoglycemic episodes are positively influenced by the low glucose suspend (LGS) feature in sensor-augmented pump therapy with no consequential rebound hyperglycemia observed. These data are seen to reassure everyone including regulatory bodies that the risk of ketoacidosis was minimal following automatic suspension of the pump.¹³ The ASPIRE in-home trial is currently under analysis, and Garg called for everyone to stay tuned for the results in the near future.

Diabetes technology is changing continuously, with advances being made almost every day. Nevertheless, implementation of technology is lagging behind, Garg concluded. He requested that when technology is applied, it needs to be kept simple, relevant to a patient's needs and safety.

CGM Technology Is Leaping Forward—What Comes Next

Michael Schoemaker, Roche Diabetes Care, Mannheim, Germany

Faith in numbers

Michael Schoemaker started his presentation by quizzing the audience on what they thought the greatest barrier was to a wider use of CGM technology in everyday diabetes practice. He offered three factors for consideration: (1) lack of accuracy of currently available devices, (2) limited user-friendliness of the systems, or (3) issues related to cost and reimbursement. He contended that *accuracy* was the fundamental property that we need to get absolutely right for CGM technology to take its proper place in diabetes practice. “What is the benefit of using a device if it's not accurate enough in a real-life setting regardless of its cost?” Schoemaker wondered. People with diabetes must have faith in the glucose numbers they see on their CGM device to ensure compliance using the technology. Physicians want reliable technology to enable them make confident and medically sound decisions. In human care, we cannot afford a leap of faith on issues of accuracy of the devices at our hand: inaccurate readings can potentially be dangerous, or at best the device is considered untrustworthy and is abandoned by its primary customer, the patient.

An accurate sensor in the making

Schoemaker revealed data on a new in-house prototype sensor being developed by Roche. To give details about this new sensor, he had to first explain the standard methods used to assess performance of CGM technology. These include parameters that measure overall clinical and analytical accuracies and sensor-to-sensor precision. It is important to remember that CGM sensors measure glucose in the interstitial fluid, not in blood. Although interstitial glucose levels tend to mirror those taking place in blood compartment, we really do not know the full details of the physiological processes taking place at the sensor-to-tissue interface, Schoemaker stated. However, to help overcome these, Schoemaker described a set of sensor design rules that have been learned over the years to enhance sensor compatibility with the subcutaneous tissue and therefore yield stable and accurate glucose monitoring. These sensor design rules include the following:

1. Sensor architecture: Multiple working electrode spots compensate for submillimeter-scale heterogeneities and processes in the subcutaneous tissues.
2. Sensor-to-tissue interface: The material and surface sensor coating enhance tissue compatibility.
3. Sensor chemistry: The working electrode contains catalyst for hydrogen peroxide oxidation, reducing interference from other electrochemically active substances.

Schoemaker presented data on two studies that compared the performance of several CGM sensors in a head-to-head fashion. In each case, two sensors of each system were implanted and used simultaneously in an effort to define sensor-to-sensor precision. Sensor performance was not only tested during regular daily living but also during hypoglycemia and periods of rapid swings in BG level to ensure precision during clinically relevant times for people with diabetes. In the first study with 12 subjects, the three commonly used sensors Abbott Diabetes Care (Alameda, CA) Freestyle[®] Navigator, Dexcom[®] (San Diego, CA) SEVEN[®] PLUS, and MiniMed (Northridge, CA) Guardian[®] REAL-Time were compared with each other,¹⁴ whereas in the other study with 10 subjects, a Roche prototype sensor was compared head-to-head with the Dexcom G4 Platinum sensor. The two studies were designed in the following manner:

- Two sensors of each system were running simultaneously in each patient for the labeled usage period. Usage period of the Roche prototype sensor was 7 days.
- Calibration and recalibrations were done according to manufacturer's labeling. The Roche prototype sensor requires initial calibration 2 h after sensor insertion and two recalibrations per day.
- Glucose swings were generated on two study days by
 - A high glycemic index breakfast
 - An altered and delayed insulin dose
 - BG readings were checked every 15 min (Roche's Accu-Chek[®] Aviva system).
- Patients were allowed to move around freely.
- SMBG reference readings:
 - On average, 17 BG readings within 24 h (Accu-Chek Aviva system)
 - During the day: one or more reading per hour
 - During night: one or two readings
 - During glucose swings: every 15 min

Study findings

Analytical accuracy is best appreciated when expressed in terms of an index called mean absolute relative difference (MARD). MARD is an estimate of the degree of agreement between CGM and SMBG readings. The lower the MARD percentage, the greater is the analytical accuracy of the sensor in question.

Compared with all other sensors studied, the Roche prototype sensor showed the best analytical performance whether measured throughout the whole range of BG readings, within hypoglycemic periods, or during phases of rapidly changing glucose levels. The Roche prototype sensor provided best overall MARD result of 9.2%, which is the first time that a CGM sensor is reported to yield an overall MARD value below the cutoff value of 10%, Schoemaker declared. Furthermore, precision parameters followed a similar pattern in favor of the Roche prototype sensor where two sensors were implanted simultaneously in the same patient and gave nearly identical glucose readings. Unlike the consistent results observed with the Roche prototype sensor, the other systems tested either showed modest overall performances or lacked sufficient accuracy at clinically relevant times, namely, critical periods of hypoglycemia or when the BG level is changing rapidly.¹⁵

Looking into the future, Schoemaker predicted that, one day, CGM technology will become a routine part of personalized diabetes management, and he is convinced of the expanding role and clinical significance of CGM systems. Enhanced accuracy and generation of clinically actionable CGM data are key features to ensure future success of CGM technology, Schoemaker contended.

When asked as to when the Roche prototype sensor is expected to be released into the market, Schoemaker offered no specific date, preferring to keep the audience in suspense.

Progress Towards Automated Glucose Control in Type 1 Diabetes with a Bihormonal Bionic Endocrine Pancreas

Steven Russell, Boston, Massachusetts

In pursuit of the ultimate prize, a man-made pancreas

Life is not so easy for people with type 1 diabetes. Current medical care is physiologically crude, physically burdensome, and emotionally demanding on the adolescents with diabetes and their families. Whether it is the need to administer MDI insulin, test BG several times a day, calculate the content of every meal about to be taken, or the type of daily chores people with diabetes have to do and contend with, all of these are often overlooked or taken for granted by many physicians and outsiders. Furthermore, the amount of daily work and inconvenience endured by people with diabetes to treat and monitor the disease does not necessarily provide a safe outcome or secure normal metabolic function. To release people with diabetes from their daily rituals and eternal obligations and bring back precious normality of everyday life in a manner that is also safe and metabolically effective would be the ultimate prescription for diabetes. Conceptually, the solution to this has to lie with the development of a fully automated glucose control system or a closed-loop system, something that apparently is not far from reality anymore, Steven Russell declared. Russell insisted that the

bihormonal bionic pancreas is only a few years away from final completion.

A fully closed-loop system consists essentially of the following components: (1) a CGM system to provide continuous measurement of glucose concentrations, (2) a computer algorithm to make insulin dosing decisions, and (3) an insulin pump to automatically deliver insulin doses. The closed-loop system used by Russell, however, also included a glucagon delivery system. The rationale behind this is twofold: (1) glucagon is the first-line natural defense mechanism against hypoglycemia, and (2) the etiology of diabetes is characterized not only by abnormal insulin secretion but also by abnormalities in glucagon secretion. Throughout his presentation, Russell showed the relevant role played by glucagon within the bionic pancreas to counterbalance insulin action and minimize the risk of hypoglycemia. Of relevance is that efforts at manufacturing a glucagon hormone preparation stable enough for use within the bionic pancreas are well underway.

The initial experiments conducted by Russell and colleagues using the bihormonal bionic pancreas in humans were positive for safety, relative simplicity, and clinical outcome¹⁶:

- Safe BG control without hypoglycemia was feasible with a purely reactive bihormonal artificial pancreas given an accurate BG signal.
- BG control for high carbohydrate meals could be achieved with only the subject's weight and BG measurements.
- Glucagon in microdoses proved to be effective and well tolerated.

In the following set of experiments, Russell et al.¹⁷ used a CGM-driven closed-loop system. The Abbott Navigator CGM system was chosen at the time as the basis for the closed-loop system, which was portable and fully automated. To overcome the physiological lag time known to occur between interstitial and BG levels, partial meal priming insulin boluses were used. The dose was calculated by an algorithm controller based purely on patient weight (i.e., without need for carbohydrate counting). Experiments were conducted in 12 subjects, were 48 h in duration, and included high carbohydrate meals and spells of exercise as challenges to glycemic control.

In those experiments, the bihormonal closed-loop control system showed an aggregate mean plasma glucose value of 158 mg/dL. Mean plasma glucose concentration at night was 123 mg/dL. Time spent in target range (70–180 mg/dL) was 68%. Time spent within hypoglycemic range (<70 mg/dL) was less than 1% overall and less than 0.5% during nighttime. In other words, the bionic pancreas worked well, maintaining impressive glycemic control with a strikingly low rate of hypoglycemia despite acute metabolic challenges.

Improving control algorithms and making it adaptive to physiological and nonphysiological signals was another area of research covered by Russell. He showed data on how the control algorithm was made to self-adapt quickly after initial glycemic exposures and how gradually with time it produced intricately appropriate amounts of insulin.

The critical test: the bionic pancreas out in the real world

Most studies reported above were done at research centers within hospital boundaries and under the gazing eyes of

nurses and physicians. However, if the bihormonal bionic pancreas were to really work and revolutionize diabetes care, it would have to prove itself to be safe and effective in a real living setting. This is exactly what Russell is planning to do in the coming sets of experiments, and a study called Beacon Hill is already underway. Individuals with a wearable bionic pancreas (operated by a smartphone system) are released into the outside world and left to enjoy life and do their normal daily activities without regulations of diet or exercise imposed on them. Going by the preliminary data presented by Russell, the promise of the bionic pancreas looks very real indeed.

Keynote Lecture: Sugar, the Dangerous Addiction—Is “Diabesity” Due to a Poison?

Robert Lustig, San Francisco, California

Barking up the wrong tree!

“The diabetes epidemic the world is seeing right now is not about obesity. There is another and more insidious culprit.” Robert Lustig challenged current wisdoms and proposed an interesting cause to the rise in diabetes and obesity rates worldwide.

Lustig argued against the exclusive concept of obesity and metabolic dysfunction. These two processes are not necessarily synonymous. Not all obese people have metabolic syndrome. In fact, numerically speaking, there are more nonobese individuals with metabolic dysfunction than obese subjects. Lustig contrasted metabolic indices of obesity with those of a patient with partial lipodystrophy, a condition characterized by metabolic syndrome with a low body fat content. Lustig argued that the “metabolic syndrome can arise from too much fat or too little fat, so therefore ‘it’s not the fat that counts.’”

Liver should be the focus of attention

Lustig suggested that metabolic syndrome should be defined in terms of the tissue where the insulin resistance resides. He said that it should not be based on absolute cutoff values of continuous clinical variables. He presented scientific data that showed metabolic disturbances were explained better by intrahepatic fat rather than visceral fat. Lustig then discussed the cellular effects of insulin at the liver and suggested that for metabolic syndrome to fully develop, there would have to be a state of selective hepatic resistance whereby insulin-induced phosphorylation of the forkhead box O1 protein is blocked, allowing for hepatic gluconeogenesis (hyperglycemia), yet at the same time allowing for the stimulation of the de novo lipogenesis pathway to promote hyperlipidemia. What could be the mechanism to block one, yet allow a second, action of insulin?

Sugar (fructose), the basis of metabolic syndrome

Lustig presented several lines of evidence to incriminate dietary sugar, the monosaccharide fructose component, as being the root cause of the ongoing epidemic of obesity and diabetes.

Dietary fructose consumption has gone up in the United States from approximately 20 g/day just before World War II to its current levels, whereby adolescents consume

approximately 75 g/day, with nearly a quarter of adolescents actually consuming 100 g/day. So currently dietary sugar seems to be a major source of total daily calories in a large proportion of the adolescent population. Lustig stressed that sugar calories are not empty calories; they have another sinister effect.

Contrary to common beliefs, dietary sugar is not the most obesogenic among the food items consumed. In a recent analysis, sugar came in third place after potato chips and French fries as the food most likely to cause weight gain. Indeed, sugar consumption made only a small contribution to excess weight equivalent to an increase of only 0.8 points in body mass index (BMI). The danger of dietary sugar does not reside with its caloric content; rather, it lies specifically within one of its two main monosaccharide components, fructose. Chronic fructose exposure promotes the metabolic syndrome, Lustig proposed.

Instead of body fat being the initial signal in the cascade of reactions responsible for metabolic syndrome, Lustig proposed an alternative model with fructose as the primary trigger leading to fatty liver with subsequent cellular and metabolic derangements. He presented two sets of data, one from animal models and the other from humans, demonstrating a close association between exposure to fructose and the development of a fatty liver. He first showed how sucrose (glucose-fructose) was conditional for the development of nonalcoholic steatohepatitis in the methionine/choline-deficient diet rat. On the other hand, exposure of the same animals to starch (glucose only) had no effect. Furthermore, recent clinical data in humans showed a close relationship between daily consumption of fructose and severity of hepatic steatosis and fibrosis in people with nonalcoholic fatty liver disease.

Lustig emphasized that fructose is a relatively toxic compound. Fructose is seven times more likely than glucose to form advanced glycation end products, and its active metabolism is known to generate reactive oxygen species, which can cause cellular damage.

The rates of metabolic disease (e.g., obesity, diabetes, and heart disease) mirror geographically those for soda (sugar) consumption throughout the world, Lustig announced. Recent data published from the EPIC-Interheart Study showed that for every sugar-sweetened beverage consumed per day, the risk of developing diabetes is increased by 22%, independent of the total calorie intake, BMI, or age.¹⁸

Indicting evidence

Lustig presented an extensive longitudinal panel analysis study on the association between diet and diabetes. In that study, Lustig and his group linked four international databases to determine what food supply predicted the prevalence of diabetes over a decade worldwide.¹⁹ Findings showed diabetes prevalence generally increased from 5.5% to 7.0% in 204 countries examined during the period 2000–2010. Only the availability of sugar predicted changes in diabetes prevalence rates. Every extra 150 kcal increased the prevalence of diabetes by 0.1%, but if the 150 kcal were consumed in form of a can of soda, then the prevalence of diabetes increased 11-fold, by 1.1% ($P < 0.001$). Although these data do not constitute a scientific proof that sugar causes diabetes, they do nevertheless fulfill the criteria for “causal medical inference” because the relationship was dose and duration dependent

and showed precedence and directionality. Obesity seemed to exacerbate but did not confound the outcome on sugar and diabetes. Lustig estimated that 25% of diabetes worldwide could be explained by sugar alone.

Overloaded mitochondria

Four items in the food supply are specifically implicated in the etiology of metabolic syndrome: trans fats, branched chain amino acids, ethanol, and fructose. These have several features in common. None requires insulin for regulation, all are metabolized solely by the liver, and none has safe nontoxic metabolic exit products, so when the substrate is provided in excess, it can readily overwhelm hepatic mitochondrial capacity. Except for fructose, Lustig noted, consumption of other items (e.g., trans fats) is either on the decline or is clinically not relevant (e.g., children do not drink alcohol). On the other hand, consumption of fructose in the form of dietary sugar remains high and is escalating worldwide.

In a unifying metabolic hypothesis, Lustig described how, with hepatic mitochondria becoming overloaded, the excess substrate is inevitably diverted to lipogenesis (fat storage). This, in turn, leads to a release of excessive fatty acid derivatives, which in themselves wreak havoc within the cell, via blocking hepatic insulin signal transduction, and secondly through generation of reactive oxygen species. The latter undermines endoplasmic reticulum function, leading to the unfolded protein response (also known as endoplasmic reticulum stress), further exacerbating defects in insulin action or secretion. Eventually, the scene is set for a florid state of insulin resistance and overt metabolic syndrome as we know it.²⁰

Bittersweet

There is no abnormality in metabolic syndrome to specifically target with drug therapy. Treatment options are confined to reduce exposure to the substrate by dietary alteration, reduce hepatic influx by eating fiber, and enhance substrate clearance by exercising. Lustig reported that there are two obstacles to eating less sugar. First, dietary sugar is addictive in nature and is not different from other addictive substances such as alcohol. Second, the food industry supplements nearly 80% of the food supply with sugar in the United States. Lustig suggested that to tackle the toxic food environment we must demand urgent government and societal interventions, but time is running out.

Continuous Intraperitoneal Insulin Therapy Using the New Accu-Chek DiaPort System—First Experience

Andreas Liebl, Bad Heilbrunn, Germany

Delivering insulin where it matters

In normal human physiology, insulin first passes the liver before it is released into the systemic circulation. It is believed this initial hepatic passage of insulin confers many advantages metabolically over the subcutaneous route of insulin administration. Insulin delivered into the peritoneal cavity and drained into the portal vein and subsequently the liver more closely follows the normal physiological route taken by endogenously secreted insulin.

The benefits of intraperitoneal over subcutaneous delivery of insulin can be summarized as follows:

- Minimal inter- and intra-individual variability
- Accelerated absorption of insulin
- Absorption unaffected by local factors (e.g., temperature, massage, physical movements)
- Avoids the risk of local inflammation in the area of the needle
- Reliable and fast insulin pharmacodynamics
- Physiological way of insulin administration

Clinically, this means less variability in glucose concentrations, lower rates of hypoglycemia, and better overall glycemic control.²¹

There are two ways to deliver insulin into the peritoneal cavity: through an implantable peritoneal pump or via port systems connected to an external insulin pump. Implantable intraperitoneal pumps have not been successful in the past because of numerous logistic and technical reasons. During the last few years, interest has focused instead on port systems for intraperitoneal insulin delivery. Liebl reported the successful application of the Accu-Chek DiaPort system.

Small study, major implications

Compared with the previous version, the current Accu-Chek DiaPort system has been improved in both design and materials used. It consists of a single-layer, soft, highly flexible catheter. The port body itself is made of biocompatible material with polyester felt for improved port ingrowth. Implantation of the device is a simple 15-min surgical procedure done with the patient under general anesthesia.

To find out safety and performance of the new Accu-Chek DiaPort system, Liebl and colleagues conducted a study using the new device in 12 subjects with longstanding type 1 diabetes. Participants had been treated with continuous subcutaneous insulin infusion but without success because of recurrent severe hypoglycemia and/or lack of improvement in metabolic control. Liebl presented preliminary findings of the first 3 months of the 1-year-long trial.

Obstacles encountered

Three of the participants had superficial wound infections at the port insertion site. However, all responded well to treatment, and the infections gradually resolved with time. Two participants had abdominal pain following initial insertion of the port, but this quickly subsided. The main obstacle encountered during the study, however, was that the catheter became partially blocked in almost all of the subjects. Flushing the catheter line with saline or changing the entire catheter seemed to provide a temporary relief of the problem. The root cause for catheter occlusion was identified as a crystallization of the insulin lispro used. This was confirmed by a mass spectroscopic analysis of the material isolated from the occluded catheters. Changing the type of insulin used became a necessity. The problem was resolved when buffered human insulin (Insuman® Infusat; Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) was used in place of insulin lispro. No additional catheter occlusion was reported during the first 3 months of the study, and only very rarely thereafter, Liebl reported. It is interesting that the use of the Accu-Chek DiaPort system was not associated with abdominal adhesions or

inflammatory reactions of any kind, unlike the case with other intraperitoneal procedures (e.g., intraperitoneal dialysis) where by complications (e.g., peritonitis) often occur, Liebl stated.

Does it work?

Liebl found the device to completely fulfill its primary objective, with 100% suitability to perform continuous intraperitoneal insulin delivery achieved in all patients studied. The Accu-Chek DiaPort system worked extremely well, Liebl announced. The success in suitability was matched by gratifying and somewhat unexpected improvements in glycemic control. The HbA1c level dropped significantly from 9.0% to 8.0%. Mean glucose concentrations and indices of glucose variability (measured by CGM) were significantly lower compared with baseline values, and the time spent within the target range increased. In addition, Liebl did not observe severe hypoglycemia occurring in any of the subjects studied during the first 3 months of the study. This finding was especially remarkable given the lower HbA1c level achieved and the known history of severe hypoglycemia suffered by many of the patients. Liebl concluded his presentation by stating that first results indicate that the new Accu-Chek DiaPort system performs well with significant improvements in HbA1c and reduced risk of severe hypoglycemia.

Going to Extremes—Addressing Low Insulin Requirements in Childhood Diabetes with Insulin Pump Therapy

Peter Adolfsson, Gothenburg, Sweden

Subtle differences between pumps mean more to kids

Recent national registry data in Sweden show the incidence of type 1 diabetes to be on the rise in preschool children. Nearly all preschool children with diabetes in Sweden are treated with continuous subcutaneous insulin infusion. The problems encountered with this age group are manifold:

- Needle phobia is relatively common among children at that age group.
- Insulin requirements can be very small (<20 units/day).
- Correction boluses are typically <0.5 unit.

Advantages of pump therapy at this age group are numerous. It allows the child to actively eat and play while attending parents can have peace of mind. Adolfsson stated, "Pumps mean less glucose variability, less risk of hypoglycemia, and are easier to handle by parents."

Adolfsson introduced the Accu-Chek Combo system as offering the following features:

- It is a two-way interactive system.
- It provides a combination of a "smart" BG meter with a reliable insulin pump.
- Bluetooth® (Bluetooth SIG, Kirkland, WA) technology is used to send information to the pump, without touching it.
- Information from both the pump and the meter can be downloaded into the Accu-Chek SmartPix device reader or Diasend system.

Which insulin pump is recommended for use in this particular age group? Adolfsson made the point that even the smallest difference in properties between pumps can

mean significant differences in outcome for children in this age group. Adolfsson gave examples of the relevant features and differences between different pumps:

- The Accu-Chek Combo system allows the inclusion of the patients' health events and activities into insulin dosing calculations.
- Although automated bolus advisors of other pump devices correct elevated postprandial glucose levels to the upper or lower limit of the BG target range, the bolus advisor incorporated in the Accu-Chek Combo system corrects to the midpoint of a preprogrammed BG target range.
- The manner in which the Accu-Chek Combo automated bolus advisor calculates remaining active insulin is another key difference among the bolus advisors, Adolfsson pointed out. Unlike other bolus advisors, it does not consider the meal-centric insulin (given to cover carbohydrate) in calculating active insulin; only the glucose-centric insulin (given to lower a high BG concentration) is used in the correction dose calculation.
- Because of their small size, infants and children with diabetes require very small amounts of insulin. A child with a weight of 20 kg may require insulin doses as little as 0.075 units/h, which could prove challenging to some existing pump systems. Adolfsson gave the following example: if a basal rate set at 0.1 unit/h needs to be reduced by 10%, 20%, or 30% as a temporary measure during an activity such as exercise, the rate could be adjusted to exactly those percentage amounts with certain pumps, including the Accu-Chek Combo system, but not with all. The reasons behind this are related to the dynamics of basal insulin release used within each pump. Basal insulin is delivered not as a constant rate as some might think; rather, it is delivered in tiny pulses, which vary in number from pump to pump. It is interesting that the number of mini-doses used to generate a basal rate may also affect the speed of action of basal insulin rate. Adolfsson showed that the time taken for a temporary basal rate to "kick in" could be as short as 8 min (Accu-Chek Combo system) or as long as nearly 1 h for other systems.
- Pump catheter occlusion tends to take a longer time to be detected in young children due to the small quantities of insulin applied. The actual time taken to activate the occlusion alarm at these low basal insulin rates is not known for many pumps. Adolfsson sought information by directly contacting the different manufacturers. Responses, however, were few and did not allow him to validly compare detection times between pumps. Disappointed with this lack of information, Adolfsson advocated that if pump occlusion is not recognized in time, this could lead to dangerous and life-threatening diabetic ketoacidosis and that this issue will therefore need to be addressed sometime soon.

Latest Innovations in Insulin Pump Therapy—A Critical Dialogue from a Technological and Psychological Point of View

Roel Hoogma, Gouda, The Netherlands, and Katharine Barnard, Southampton, United Kingdom

In this lecture, delivered in dialogue format, both Roel Hoogma and Katharine Barnard presented their views on the

value and limitations of each of the recent innovations in pump therapy. They suggested ways to improve the clinical and psychological well-being of patients using the pumps.

He said, she said

The bolus advisor. Hoogma likes the bolus advisor as it helps patients who would otherwise struggle to manually calculate the insulin dose. He posed the question, "Do we really have the evidence that the bolus advisor makes a difference to overall metabolic control?"

Barnard saw several psychological benefits associated with the use of the bolus advisor such as a reduction in stress and improved self-confidence.²² Barnard posed some questions that need clarification: "Do you have to use your bolus advisor every time you have something to eat?" and "Who should decide on the parameters used to calculate boluses?"

Sensor-augmented pump. Hoogma made the point that CGM sensors would have to be used at least 75% of the time to be of relevant clinical benefit, and where do we stand if the patient decides to wear the sensor only intermittently? Hoogma suggested that patients might become too comfortable and overtrusting of the system and forget to make adjustments for their daily events and activities.

Barnard saw the "arrows" on the meter that indicated the trend of the BG was well liked by patients. It was important for patients to feel confident and to be "in control of their diabetes." The sensors require less BG testing, Barnard stated. She warned against using sensors as a tool to detect bad behavior in adolescents. She reminded the audience that life is hard enough for these kids living with diabetes without the need for them to also be reprimanded.

LGS. Hoogma raised some concerns (e.g., "Is the LGS feature truly useful and do we have the scientific evidence to show benefits?" and "Do we really get less hypoglycemia with LGS?").

Hoogma wondered whether a simple alarm system to warn the patient of an impending hypoglycemia event that would prompt the patient to take a carbohydrate intake would be better than the automatic threshold suspension of the pump itself. He argued that stopping the insulin infusion would not necessarily mean stopping the action of insulin, which will continue for another 2 h. Other experts in the audience disagreed with Hoogma and said that it would make sense for them to stop insulin infusion when blood sugar is running dangerously low.

Barnard could see the clear benefits of LGS in addressing the issue of hypoglycemia: "Fear of hypoglycemia is real, pervasive, and disabling to patients and their families." LGS pumps may curb maladaptive behavior often used by patients to avoid hypoglycemia such as allowing BG to drift to high levels or deliberately reducing insulin doses. The importance of accuracy and trust in the device was another issue touched on by Barnard.

Remote control. Hoogma wondered, "What would happen if the patient forgot to carry the remote control; how would the pump continue to operate?" Hoogma questioned the convenience of having to carry two cell phones at the same time. In his opinion the device would have to be small and efficiently fast to be useful.

Barnard enthused that “it is fantastic to have a remote control device as it is discrete, takes away that visibility of the disease and plenty of people carry two mobile phones without any problem!” She reiterated that the remote control device “takes away the badge that says I’m different from everyone else.” Barnard agreed with Hoogma that the connectivity between the pump and the device needs to be made fast and efficient.

Bolus types. According to Hoogma, there are no publications on the benefits of using different types of boluses. What bolus to use, when to use it, and whether boluses actually replicate normal physiology are the type of questions awaiting answers.

Barnard concurred with Hoogma but suggested potential benefits that increase patient confidence and gives them greater freedom in sports activity.

Basal rate. Hoogma questioned current practices: (1) What’s the point of having a changeable basal rate when in reality patients often go years using the same basal rate? (2) Some patients tamper with basal rate almost every hour, others stick with the same rate all day. Where is the scientific evidence that considers 24 different basal rates better than having a single basal rate? (3) Do we know the time of onset of the metabolic effect when we change the basal rate? Hoogma presented his own clinical experience and said that changing the basal rate had no effect of any kind on the metabolic outcome of the patients he observed.

Barnard felt changing the basal rate helped patients “fine tune” diabetes control and reduced the risk of having “out of range” blood sugars. It also gave people with diabetes greater confidence managing their disease.

Connectivity/data management. Both speakers indicated this was a gray area in pump management. Hoogma saw a clear need for new software programs to be developed (e.g., to guide patients on the use of different insulin boluses).

While a “huge fan” of data management and bolus advisors, Barnard still felt uneasy about who should be in control of the data and called for proper education of both patients and staff in this regard.

Summary

Hoogma and Barnard presented a healthy and successful debate in that the bad as well as the good of each device were brought to light. At times, the debate looked like a contest made between the consummate clinician (Hoogma) and the compassionate psychologist (Barnard). At the end, both Hoogma and Barnard agreed that insulin pump therapy is here to stay and that the future looks promisingly bright.

Mass Spectrometry Is Used as the Reference Procedure to Calibrate Accu-Chek Blood Glucose Meters—And This Is Clinically Important

Rolf Hinzmann, Roche Diabetes Care, Mannheim, Germany, in collaboration with Matthias Appel, Roche Diabetes Care

Why do we need standardization?

Before the time of standardization people were well aware that arm’s length, pounds, and gallons had different

meanings at different times and in different places. Today, we have exact definitions for meter, kilogram, and other units of measure. An example is the primary kilogram, consisting of platinum and iridium, that by definition has a mass of 1 kg and is hosted by the Bureau International des Poids et Mesures (BIPM) (International Bureau for Weights and Measures) in France. The idea behind standardization is that measurement values are reproducible and independent of the (1) time and (2) location where they are produced. To make sure that finally all measurement devices produce identical or similar results, it is necessary to establish traceability to a primary standard or reference material, such as the primary kilogram, which is achieved through a series of calibrations.

What is a traceability chain?

For illustration, we use a simple example: scales for professional use need to be traceable to the primary kilogram. The BIPM uses the primary kilogram to calibrate very accurate scales that are used to assign weight values to copies of the primary kilogram. These are then used by national metrological institutes (such as the National Institute of Standards and Technology in the United States) to produce further copies for the purpose of calibrating professional scales, etc. However, the further down one moves along the traceability chain, the higher are the potential deviations compared with the primary kilogram. The weight value delivered by a scale used for patients in a hospital will have a considerably higher measurement uncertainty than a measurement performed with a sophisticated scale at the BIPM.

How does standardization work in the case of BG concentration?

For glucose, the highest reference standard is the so-called standard reference material (SRM) 917, which is a glucose powder of very high and well-defined purity ($99.7 \pm 0.3\%$). This material is used at Roche to calibrate the most accurate method to measure glucose in blood that is currently available: isotope dilution-gas chromatography mass spectrometry (ID-GC/MS). Currently, Roche maintains the only industry laboratory that has an accreditation as a calibration laboratory for glucose. As ID-GC/MS is very expensive and time consuming, this method is not used to directly calibrate Accu-Chek BG meters. Instead, it is used to calibrate a faster and less expensive enzymatic (hexokinase) method on a Roche cobas[®] analytical system, which is then used to calibrate the Accu-Chek BG meters. The calibrators used to calibrate the Accu-Chek BG meters are sets of whole blood patient samples. Both ID-GC/MA and the hexokinase method are reference measurement procedures recognized by the Joint Committee for Traceability in Laboratory Medicine and listed as such on BIPM’s Web site (www.bipm.org/). Reference measurement procedures must have a very high quality and low measurement uncertainty. By using this calibration procedure, BG values measured on Accu-Chek BG meters are directly traceable to SRM 917.

What is a matrix effect?

One important factor has to be considered: although SRM 917 is a white powder, glucose in blood is part of an entirely different matrix containing water, electrolytes, metabolites,

and blood cells, which have an impact on the measurement. To a certain degree, the matrix always impacts on the measurement result, a phenomenon that is called the matrix effect. To avoid this effect, it is important to convert the blood samples and the SRM 917 into the same matrix. This is achieved at the high end of the traceability chain by dissolving the SRM 917 in water. In the following calibration steps, the whole blood samples are deproteinized by adding perchloric acid. The same steps are applied to the SRM 917 solution. This procedure guarantees that no or very little matrix effect is introduced into the measurement.

How can a matrix effect affect calibration?

Although most manufacturers calibrate their BG meters to SRM 917, currently only few are using ID/GC-MS in their traceability chain. Most other manufacturers use the so-called YSI method (Yellow Springs Instruments, Yellow Springs, OH) to calibrate their BG meters. This method is not recognized as a reference measurement procedure by the Joint Committee for Traceability in Laboratory Medicine. Comparative measurements (data on file) at Roche in Mannheim have demonstrated that for blood samples there is a systematic difference of approximately 4% between ID-GC/MS and the YSI method. As this difference is not observed when aqueous samples are being compared, it could be due to a matrix effect of the YSI method.

Why is a very high quality of the calibration procedure clinically important?

Several studies using simulation modeling have shown that inaccurate measurements with BG meters can lead to wrong insulin dosing, missed hypoglycemia, erroneously induced hypoglycemia, increased glycemic variability, and perhaps even an increased HbA1c level. Although the models applied were quite different, all of these studies came to the similar conclusion that an analytical error below 10% had almost no impact and that an error of 15–20% led to increased incidence of the above-mentioned outcomes.^{23–26} A calibration bias of 4% already consumes a significant portion of the desirable analytical error and leaves less space for other inherent error components such as random error, interferents, influence of temperature, humidity, and shelf life.

Therefore, a very high quality of the calibration procedure is of utmost importance. It will become even more important when future regulations foresee more strict requirements for the allowable analytical error.

Analytical Performance of Blood Glucose Meters—Why Is It That Comparative Accuracy Evaluations Frequently Yield Differing Results?

Gary Thorpe, Birmingham, United Kingdom

Establishing analytical performance of a BG meter is not as simple as some people might think. Studies comparing accuracies of different BG meter systems are only appropriate and meaningful if they adhere to internationally set standards and norms. Differences in accuracy between BG meters can sometimes be due to errors introduced during the assessment process and so are not necessarily the “meter’s fault.” Furthermore, being Conformité Européenne (CE) marked should not be seen as providing full proof of accuracy of any BG

meter. It should suggest that the device also needs to be tested in real day-to-day use. With these introductory remarks, Thorpe set out to outline two main issues: (1) the general processes involved in evaluating accuracy of BG meters and (2) to provide useful hints for clinicians on how to understand and critically interpret publications of accuracy studies.

Thorpe’s accuracy checklist

In an effort to make sense of the increasing number of publications on the accuracy of BG meter systems, Thorpe developed an easy-to-use but also rigorous and uniform checklist to help clinicians verify the quality of accuracy studies published. He identified pitfalls and interferences responsible for inaccurate or discrepant results. Using the checklist in a survey of recently published studies, Thorpe found that only 20% of accuracy studies had passed the checklist test and 40% showed deviation from internationally set standards and guidelines (International Organization for Standardization [ISO] 15197).²⁷

Thorpe’s accuracy checklist consists of the following components:

- Comparison method
- Comparing “like with like” samples
- Number of samples
- Spread of glucose concentrations
- Accuracy criteria
- Number of strip lots
- Full details provided
- Independency
- Concordance with ISO 15197

The use of an appropriate comparison method, of known total error and traceability, is critical in ensuring a correct comparison and avoiding potential bias. The comparison method should be the one stated by the manufacturers.

Not comparing “like with like” samples can lead to misleading differences between studies. As an example, Thorpe showed a correlation graph of capillary versus venous blood samples taken in the fasting and postprandial state. It showed close correlation between samples taken during the fasting state but poor correlation for postprandial samples, with differences up to 3 mmol/L observed.

Correct minimal timings between specimen collection and analysis presented another common limitation.

A sufficient number of freshly obtained capillary samples (> 100) should be used, covering the wide glycemic range, and tested in duplicate.

Proper analysis and presentation of results are another important consideration. Information should be derived from several lots of test strips to demonstrate consistency and general applicability of findings. Differences between meters should be plotted against the comparison method used and assessed for clinical accuracy such as by the Parkes error grid analysis.

The current version of ISO 15197 defines accuracy by the percentage of results within ± 15 mg/dL (0.83 mmol/L) for glucose values < 100 mg/dL (< 5.6 mmol/L) and within $\pm 15\%$ for glucose concentrations ≥ 100 mg/dL. Even tighter acceptance criteria (within 10 mg/dL and 10%) have been proposed, Thorpe remarked.

Because of the lot-to-lot variability in strips (sometimes responsible for as much as 5–10% bias in differences found

between systems), several different lots (ideally three) need to be used. In the words of Thorpe, we need to be sure of the consistency of the day-to-day performance, instead of just taking a random snapshot.

Concluding his talk, Thorpe emphasized the point that BG meter system accuracy studies should be interpreted with caution. Reported differences between meters can sometimes be unreliable or misleading. The checklist presented above should help the clinician arrive at the right conclusion.

Not All Commercially Available Blood Glucose Meters Show Acceptable Analytical Performance

Andrew Hattemer, Roche Diabetes Care, Mannheim, Germany

The markets are awash with BG meter systems of all kinds and qualities. Patients can easily pick the one they like, that is cheap, and without the need for a prescription, just like they are buying a new mobile phone.

However, an inaccurate BG meter system can result in erroneous results and lead to real health risk for the individual. Clinicians should be aware of the different qualities of BG meter systems available in the market, and they have the professional responsibility to advise their patients appropriately.

Picking the right meter

Hattemer identified three recent studies that investigated the analytical performance of a large collection of commonly used BG meter systems—to isolate the good systems from the bad ones.^{28–30} The studies have been undertaken by independent and reputable research and technology institutions and were conducted in line with international ISO standards and guidelines. Hattemer presented the analysis of the three studies and gave his own verdict on the subject.

Two of the studies analyzed were conducted at the Institute of Diabetes Technology at Ulm, Germany, and the third was performed at the Rainier Clinical Research Center, Renton, WA. The variety of systems tested included some made by established manufacturers and others marketed as low-priced devices. The systems were selected based on relevance to the market, CE approval, and, in the case of the U.S. study, Food and Drug Administration approval. Forty-three systems were investigated in one study, whereas seven and five systems were used, respectively, in the other two studies. One single lot of test strips was used in the larger study, whereas multiple strip test lots (three or four) were analyzed in the two smaller studies.

The method used to assess the quality of the BG meter systems conformed to the ISO 15197:2003 standard in all three studies. The results of each SMBG measurement were compared with the result obtained by the comparison method procedure specified by the manufacturer of the SMBG system in question (e.g., for Accu-Chek systems to use the cobas 6000 c 501). Results were included for analysis if the experiments fulfilled the recommended testing procedures of ISO 15197:2003 (e.g., the recommended number and distribution of samples). It is noteworthy that the accuracy requirements of the current ISO 15197 guideline are even tighter than the ones of the recent ISO 15197:2003 standard. Systems tested were analyzed for fulfilling the accuracy requirements according to both current and recent ISO 15197 standards.

Outcomes

Single-lot study. Nine of the 43 systems tested could not be completely evaluated because of the nature of the method used to measure the BG within these systems. Apparently, at very high or very low BG concentrations, these systems became vulnerable to oxygen sensitivity, precluding accurate assessments in these concentration ranges.

Of the remaining 34 meter systems that had been fully evaluated, seven (20.6%) failed to meet the current ISO standard. When the new draft ISO standard was applied, 16 systems, or nearly half (47.1%) of the systems tested, failed to pass the new criteria. Several of the low-priced systems failed the existing ISO standard, and very few “survived” the new stricter ISO standard criteria. Hattemer made the point that failing the new ISO standard was not confined to the low-cost meters. Several of the systems made by established manufacturers had also failed. By contrast, all Accu-Chek BG meter systems topped up the ranks for good performance, Hattemer reported.

Multiple-lots studies. Because of the known impact of lot-to-lot variability on indices of accuracy, the findings of these two studies carry additional significance. The low-price system that had passed earlier tests now failed on the multiple-lots test analysis. When accuracy results from the four- and three-lot assessment study were scrutinized further using the current ISO 15197 standard, only one meter system passed the full test: the Accu-Chek Aviva system.^{30,31}

Hattemer concluded his talk by stating that only the Accu-Chek Aviva system had successfully passed all three hurdles: the lot-to-lot variability, the within-lot variability, and the important issue of bias.

The Importance of a Structured and Continuous Feedback Loop in Diabetes Management

Raimund Weitgasser, Salzburg, Austria

The world is changing in so many ways, in both the field of technology and innovation. Provision of an effective health-care system is now a priority for all governments and stakeholders. Noncommunicable or chronic diseases represent a heavy and an ever-increasing burden on human health and economic growth. Diabetes exemplifies the case of a chronic and burdensome disease. But, diabetes can also serve as a platform to explore new ideas on how personalized medicine can enhance the healthcare outcome. One such idea is to combine patient empowerment with innovative technology as part of diabetes management. This is precisely what Weitgasser and his European partners decided to do recently.³¹ Weitgasser shared the idea of how structured SMBG (structured testing) within the context of a continuous feedback loop system can improve diabetes outcome.

Weitgasser started by asking three specific questions related to the principle of structured SMBG:

1. Does structured testing improve glycemic control?
2. If glycemic control is improved, does it also improve other non-glucose metabolic parameters?
3. Can technology be used to enhance communication between patient and doctor?

Needless to say, Weitgasser affirmed the benefits of structured testing on all three issues asked above.

He first introduced the work published by Polonsky et al.³² This group examined the effectiveness of structured testing on glycemic control in poorly controlled non-insulin-treated people with type 2 diabetes. The 12-month long trial showed a significant difference in HbA1c (0.5%) in favor of structured testing.

Weitgasser then made the point that the benefits of structured testing were not confined to improvement in BG levels alone. SMBG combined with proper education and personalized feedback for adaptation of treatment can lead to improvements in weight, BMI, and waist circumference. This was supported by the findings of the ROSSO study.³³ Moreover, the glucometabolic benefits of structured testing seemed to last with time.

With regard to the third issue of the role of innovative technology as a means of improving SMBG performance, Weitgasser drew attention to the recent findings of the VISION study.³⁴ This study examined the effects of displaying SMBG information graphically using the Accu-Chek SmartPix system on glycemic control and physician-patient dialog. The study was a prospective, 6-month, multicenter, observational study that included people with type 1 and type 2 diabetes attending 129 practices in Germany.

The VISION study showed that the graphical presentation of SMBG data to patients resulted in a significant reduction in HbA1c in both types of diabetes. The study also showed remarkable improvement in the doctor-patient communication: doctors reported achieving better communication with patients in 76% of the cases, and treatment targets seemed easier to achieve.

Six steps to success

Six individual steps make up the complete structured feedback loop.³¹ Each step has been shown in dedicated studies to be of clear and proven benefits. The driving force within the entire loop system is information related to BG levels. Weitgasser also stressed the fact that to gain maximum benefits, the cycle would have to be repeated continuously:

1. The patient receives structured education and training on how to perform "structured testing." The patient is taught to measure BG levels at specific times during the day or related to specific activities to immediately understand the effect on the BG concentration.
2. Structured testing is conducted to monitor the patient's glycemic status.
3. Electronic devices or software tools are used to collect and document SMBG data directly from the BG meter. This information is stored in a personal health record and viewed by patients as well as the healthcare providers.
4. Data analysis is presented graphically, illustrating findings in an easy-to-digest manner. Direct patient support for targeted decisions about day-to-day self-care is provided (i.e., adaptations in lifestyle or medication).
5. Treatments are chosen based on the characteristics of the individual patient and the SMBG profile to achieve individualized treatment goals.
6. Treatment efficacy is assessed on a regular basis. If the treatment target was not achieved, the patient would be subject to reinforced and perhaps restructured education.

Thus, personalized diabetes management becomes a perpetually revolving cycle that is repeated for the patient every now and then, at varying time intervals.

Weitgasser reminded the audience of the recent position statement made by the American Diabetes Association/European Association for the Study of Diabetes organizations that called for a "personalized approach" to the management of diabetes. It seems that the feedback loop concept of Weitgasser and colleagues could not have come at a better time.

The Impact of Strip-Free SMBG Technology on Patients' Adherence to Recommended Test Frequencies—Results from the ExAct Trial

Alberto Maran, Padua, Italy

Alberto Maran had one specific mission in mind for his presentation: he wanted to share with us the interesting findings of the ExAct Study.

SMBG—more is better

International diabetes organizations recommend routine SMBG testing in insulin-treated people with diabetes. The optimal number of tests may vary between organizations, but most suggest at least three tests per day. All agree on the clinical benefits associated with regular SMBG testing. Maran presented several lines of evidence showing a close relationship between frequency of SMBG testing and metabolic control (HbA1c).³⁵ In one example, he showed how one additional SMBG test per day led to improvement in HbA1c of 0.32%. The maximum reduction in HbA1c was seen when 10 tests were done per day.⁶

However, despite the obvious benefits described above, many patients fail to do sufficient SMBG testing. In some studies, more than 50% of the patients questioned said they did not follow the recommended SMBG guidelines.³⁶ Maran indicated there were several barriers to patients' adherence to SMBG testing. He explained that patients would test more frequently if the testing procedure was made easier, more discrete, and less painful. If that was the case, Maran asked, could using an integrated and strip-free device such as the Accu-Chek Mobile system help people with diabetes to adhere better to SMBG testing? The answer to that lies in the results of the ExAct Study.

ExAct Trial: more than a numbers game

Earlier experience with the integrated Accu-Chek Mobile system had been encouraging. In one previous study, the use of the device doubled the rate of SMBG testing in nonadherent people with diabetes.³⁷

Maran first explained the nature and design of the ExAct Study. The study had been conducted in four countries: Germany, Italy, The Netherlands, and the United Kingdom. Some 478 nonadherent (<3.25 tests/day at baseline) insulin-treated people with diabetes were enrolled and followed up prospectively for 6 months. Based on the treatment center, they were randomized to either "integrated strip-free" or any "single-strip" SMBG system.

Results

The average testing frequency increased significantly in people using the Accu-Chek Mobile system. After correcting

for statistical adjustments, the difference in SMBG testing amounted to an extra 0.4 tests per day (2.5 tests per week) in favor of the Accu-Chek Mobile system.

As far as glycemic control was concerned, both treatment groups showed an initial drop in HbA1c level. However, people using the strip-free Accu-Chek Mobile system had a significantly greater HbA1c reduction (0.2%) compared with those using the single-strip SMBG system. The improvement in glycemic control was even more pronounced in people with type 2 diabetes.

Conclusions seemed clear and easy to make for both Maran and the audience at large. People with diabetes are more willing to do more SMBG tests if offered a strip-free BG meter device. The metabolic benefits observed with the Accu-Chek Mobile system tell an additional story: the impact of using the device is more far-reaching than a mere increase in the number of SMBG tests performed.

The Psychology of Eating Behavior

Alfred Janis Sipols, Riga, Latvia

Alfred Janis Sipols took the audience on a fascinating journey of the human eating behavior: how we develop preferences to food in general and the complex interaction between biology and culture in shaping our taste. In addition, he offered therapeutic remedies to bad eating behavior.

Sipols' opening statement was that the world as a whole was eating badly. Rates of obesity are escalating almost everywhere. In the developed world, food is abundant in quantity and with a big variety of the wrong kinds. Mass media and globalization exacerbate bad eating habits. A sedentary lifestyle is rampant in western societies. The situation with regard to obesity is not any better in the developing world. The negative effect of mass media and high caloric density seem to have reached the remotest parts of Africa.

Is ice cream an acquired taste?

Several factors apparently control the way we develop food preferences in life. First, there are biologically set hard-wired central nervous system feedback systems that we have in place and have no control over. For instance, if the body is physiologically deficient in an element such as sodium, we then start to taste salty food better and consequently eat more of it in an attempt to replace the missing element. In fact, even if the missing element is not known to have a specific taste (e.g., vitamins), animals tend to somehow veer towards eating food rich in the element they are deficient in. Why most people indulge in sweet-tasting food, however, is another story altogether, Sipols explained. This is because in evolutionary terms, sugar represented an inexpensive and immediate source of energy to consume. Inadvertently for mankind, this "evolutionary reflex" is also an indelible biological system.

Although biology may have a part to play, personal psychology and social exposure seem to be a bigger culprit. "I wasn't sure what to make of ice cream the first time I tried it, but I surely was a big fan of it by the third time," Sipols admitted, making the point how social norms and repeated exposure shape our preferences for food. In addition, modalities of food (appearance, taste, flavor, sound, texture, temperature) and the environmental cues of meals (timing,

location, socialization) represent another important drive for food preferences.

Watching big brother

Sipols drew attention to the importance of early experience in life with food. Apparently, we get conditioned to either approach or avoid certain foods depending on the "positive incentive value" of the messenger and background setting. Sipols quizzed the audience whom they thought a young child would most likely emulate in eating habits: parents, siblings, relatives, friends, teachers, pediatricians, or heroes? According to Sipols, an elder sibling serves as the best role model for a child making food choices. Sports "heroes" came in second place, whereas "parents" were a distant third.

Later in life, we draw heavily on the social norms and prevailing culture as we develop acquired tastes for food, whether it is eating spicy food, pungent cheeses, or drinking alcohol. At this late stage in life, biology plays a very little role. In some sense, we only have ourselves to blame. However, addiction to food tends to be perpetuated biologically by the brain reward system that is not different to that seen with a chemical addiction.

Changing behavior—easier said than done

Sipols identified two main approaches for tackling unhealthy eating habits: information and motivation.

Information can be presented in a negative way to highlight the dangers associated with bad behavior (e.g., health and social stigma associated with obesity and risk of development of medical diseases such as diabetes and heart disease). Positive valence, on the other hand, includes information material and educational campaigns to promote social and health benefits of certain foods.

Motivation is a harder task to pursue, Sipols conceded. Whenever a change in behavior is contemplated, patients always tend to weigh in the costs (e.g., inconvenience, bland taste) versus benefits (e.g., reduction in risk of disease). Furthermore, unlike the case with young children, there is generally no role model figure for adults. Instead, self-help groups seem the best alternative method in adults (e.g., Weight Watchers and Alcoholics Anonymous). Sipols sincerely believes that the best prescription to changing eating behavior is "to give patients successful role models in non-threatening emotional atmosphere in the form of self-help groups."

Mental Contrasting and Implementation Intention (MCII) Are Validated Tools to Improve Behavioral Change in Chronic Disease

Gabriele Oettingen, New York, New York

Oettingen reviewed the question, "Is it nice to dream every now and then and just try to think positively?" "Better not," she affirmed. "Thinking positively" may bring momentary happiness to the individual but in the long term can cause more harm and can even predispose the individual to become more depressed. Worse still, the future you envisioned may never arrive if you only think positively. A whiff of reality with a clear recognition of obstacles to overcome is necessary to reach the desired future target. Is there an alternative behavioral technique that allows you to enjoy the sentiments of

your dreams but enables you to work effectively and successfully to fulfill those dreams? “Yes,” Oettingen said, “it is called mental contrasting.”³⁸

Wish—outcome—obstacle and plenty of imagination

The idea of mental contrasting, developed by Oettingen and colleagues, is very simple: you imagine the desired future you want and mentally contrast that with the realities of daily life, which leads you to decide on the prospect of success. If success is likely, this mental strategy helps strengthen your energy and efforts toward attainment of that future. If, on the other hand, reaching the future is deemed unfeasible, mental contrasting helps you to quietly disengage and walk away to do something better in life. So mental contrasting is a strategy “to help you clean up your life, to go for the things that are promising, and avoid complete dead ends,” Oettingen said.

Evidence has shown the benefits of mental contrasting. Mental contrasting has worked for people dealing with academic or professional wishes and concerns, with interpersonal relations, or health-related goals.³⁸

Oettingen presented the results of a series of mental contrasting experiments demonstrating an improved outcome:

- Healthcare managers trained in mental contrasting managed everyday life matters better than the control group (who only used positive thinking).
- People with diabetes trained in mental contrasting showed enhanced diabetes self-management (diet, weight, and exercise) compared with a control group who only positively indulged in the future.
- Overweight middle-aged men reformed their physical activity and dietary habits within 1 month of using mental contrasting.

The benefits of mental contrasting are not limited to the examples cited above but extend to other domains of life, anything from smoking cessation to efforts at acquiring a new language, Oettingen explained.

It is the intentions that count

The benefits seen with mental contrasting can be maximized further if combined with another procedure called implementation intentions.³⁹ This if–then planning equips the individual to effectively overcome the obstacle and to stay on target for reaching the desired future.

Mental contrasting with implementation intention (MCII) can be used as a strategy to fight bad habits. In one set of experiments, MCII was tested for effectiveness in diminishing unhealthy snacking habits among students. It proved successful as participants in the MCII group consumed fewer unhealthy snacks compared with participants who used either mental contrasting or formulated implementation intentions alone.⁴⁰ Oettingen gave other examples whereby MCII was shown to improve behavior in relation to exercise, stress at work, performance at school, or curbing alcohol consumption.

Oettingen stressed that MCII is completely different from traditional behavioral interventions. MCII does not focus on heightening incentives and strengthening expectations. It teaches the individual meta-cognitive self-regulatory strategies for effective goal pursuits. It is something you can learn independent of coaches, trainers, and therapists. “You can

apply MCII to any of your wishes you may have”; what’s more, “you will finally act on them,” Oettingen concluded.

So it seems that if you really want to be serious about the future, don’t just dream about it, try MCII!

Different Steps and Ways of Implementing Structured Testing—There Is No “One Fits All” Approach

Matthias Axel Schweitzer, Roche Diabetes Care, Mannheim, Germany

It is important that the medical community gains sufficient insight into how people in industry think and operate to ensure an open, trustful, and most fruitful collaboration with academic science and research. We had an opportunity to hear the views of one such personality, Matthias Axel Schweitzer, Head of Global Medical and Scientific Affairs at Roche Diabetes Care. Although the main topic of his presentation was structured testing, he nevertheless managed to shed light on the issues that drive development and innovation at the company. He gave professional perspectives on the current state of diabetes care and what the future might hold for diabetes technology and management.

Schweitzer’s opening remark was this “we are not here just to sell smart technology devices to people with diabetes, we also want to see those products make a difference to diabetes management.” “Our aim is to enable diabetes management,” Schweitzer emphasized repeatedly. This statement might have been considered as a common slogan used by the industry, but as we carefully listened to the evidence presented; we quickly realized Schweitzer truly meant what he said.

Schweitzer identified four areas of work whereby glucose information can be used to enable diabetes management:

1. Technology—we have a solid foundation

Technology provides the basis of diabetes devices and products. “Technology has to be built on a sound foundation,” Schweitzer declared. He believes glucose information can only be considered “true” and “reliable” if the devices used have accomplished a *total* system performance. “All performance factors must be considered and completely fulfilled,” Schweitzer stressed. High accuracy of a device becomes meaningless if the safety is in question. Reviewing recent evidence, Schweitzer had to take pride in the impressive performance achieved by Accu-Chek BG meter systems.^{28–30} He also made reference to the Roche CGM sensor in development as a promising new device soon to be offered.

2. Clinical value—we go the extra mile

Clinical application of a medical device requires compliance with general medical standards. “We do that routinely but we also try to bring extra clinical value to the devices we offer,” Schweitzer affirmed. He provided the core strategy with two successful examples to demonstrate: the integrated strip-free Accu-Chek Mobile system and the automated bolus advisor.

Schweitzer described in detail the role of SMBG and CGM testing in the management of diabetes and reiterated the close correlation known to exist between frequency of SMBG/CGM testing and glycemic control.^{6,9,32,36}

Schweitzer suggested that SMBG testing would be of limited clinical value only unless two things happened:

1. Testing is done at specified and clinically relevant times.
2. Information gathered can lend itself to clinical interpretation and therapeutic action.

He offered, "What good are BG measurements if in the end they only represent plain numbers that neither the patient nor the doctor knows what to do with?" BG testing needs to be *structured* to be useful in diabetes management, Schweitzer indicated. Clinical experience has shown two likely benefits to structured testing: (1) it improves glycemic control, and (2) it provides opportunity for therapy adjustments. The evidence for this has been shown by the STeP study as well as by others.^{32,41}

On the issue of which of the existing SMBG profiles should be adopted in clinical practice, Schweitzer offered no specific preference. He indicated that the nature of a glucose profile (i.e., times and number of glucose tests) should be individualized depending on the clinical situation of the patient, country, culture, prevailing diabetes practice, etc. "No one size fits all." Several different SMBG profiles have been successfully applied.⁴²⁻⁴⁵ He acknowledged, however, the increasing popularity among physicians of using a seven-point glucose profile (originally introduced at the STeP Study³²) for people with diabetes, including those with type 1 diabetes. It is interesting that recent evidence has shown this SMBG profile to be almost as good as CGM testing when the two systems were compared together in people with type 2 diabetes. The REACT3 Study demonstrated comparable reductions in HbA1c by both systems. CGM testing performed slightly better and had less incidence of hypoglycemia than the seven-point profile.

3. Medical devices—part of a bigger picture

Glucose monitoring information cannot be processed if it is isolated from the other elements of diabetes management. We have to view the global information of diabetes management and see the bigger picture, Schweitzer explained. A good example of this is the structured feedback loop.³¹ Schweitzer further suggested that to improve services in the future, the different elements of diabetes management should be technologically interconnected and, at least partly, Web-enabled, with the information free for all so that everyone can see the full picture.

4. Automation—making life easier for patients

Schweitzer reminded everyone how the electrocardiograph originally started. Today we do not just see multiple spikes on a piece of tracing paper; in fact, we see a fully automated function. It includes data capture, data analysis, and clinical diagnosis all neatly packed together. He hoped the same could be applied to future management solutions in diabetes. We should not abandon people with diabetes or burden them with excessive daily tasks, Schweitzer insisted. Repeated tasks and tedious homework require a considerable amount of energy and motivation. Patient motivation is not easy to initiate and is even harder to maintain in the long term. Automation reduces the daily burden of the disease, provides relief and guidance to patients, and enhances overall diabetes care. The automated bolus advisor is one such example. An automated pancreas would be the ultimate aim.

Use of an Insulin Bolus Advisor Improves Glycemic Control in Patients Not Achieving Optimal Control Using MDI—Results of the Automated Bolus Advisor Control and Usability Study (ABACUS)

Ralph Ziegler, Muenster, Germany

The main principle of MDI therapy is to inject insulin with each meal consumed. The amount of insulin required is based on the calculations of several factors. These factors include insulin to carbohydrate ratio (I:CHO), insulin sensitivity factors (ISF), and current target BG concentrations. Patients are expected to do these calculations mentally before each meal. The process is time consuming, and there is a risk of making mistakes with potentially serious clinical consequences. Not everyone is adept at doing mathematical calculations "in their head."

The automated bolus advisor has been used successfully to circumvent this issue in people using insulin pump therapy.⁴⁶ It has been tested in people on MDI therapy, and it maintains glycemic control without changing the insulin dose or weight.⁴⁷ The bolus advisor has been reported to bring self-confidence and peace of mind to people using it.²²

ABACUS

This was a 6-month randomized controlled study undertaken by Ziegler and his colleagues to investigate the Accu-Chek Aviva Expert meter system with an automated bolus advisor in people with diabetes treated with MDI therapy. The group wanted to know the effect of the bolus advisor on metabolic control and treatment satisfaction.

Two hundred eighteen people with diabetes with suboptimal glucose control were randomized into either using the bolus advisor or manually calculating prandial insulin doses. At baseline, the patients had an MDI competency assessment (e.g., carbohydrate counting) and psychological evaluation, which was repeated at the end of the study. Approximately 50% of the patients in each group received CGM testing at baseline and on follow up. The goal of the study was a reduction in HbA1c of >0.5% in all patients.

Main results

More subjects in the bolus advisor group achieved reduction in HbA1c level of >0.5% than in the control group (56% vs. 34.4%, $P < 0.01$). There was significantly less glycemic variability associated with the use of the bolus advisor (−20% vs. −2.9%, $P < 0.01$). It is important that the concomitant reductions in HbA1c and glycemic variability did not come at the expense of exacerbating the risk of hypoglycemia: the frequency of hypoglycemia was not different between the two groups. People using the bolus advisor reported significantly higher rates of satisfaction with treatment compared with the control group.

Finer details

Ziegler reported three additional and very interesting findings of the study:

1. Did the intervention group actually use their bolus advisors? Yes, Ziegler replied, 76% of the time. Patients used the bolus advisor almost three times a day and seldom declined the advice offered. Participants had

great faith and satisfaction in the bolus advisor, Ziegler suggested.

2. Use of the bolus advisor seemed to have encouraged the attending physician to intervene and modify parameters such as insulin sensitivity and the I:CHO ratio. This highlights the point that when information becomes readily available, it will invite therapeutic action.
3. The biggest surprise to Ziegler was not the success observed in the bolus advisor group but what happened in the control group. When Ziegler reviewed the records of the bolus calculations of patients in the control group to see if the I:CHO and ISF calculations had been done mathematically correctly, he found the following: 53% of the I:CHO and 74% of the ISF calculations were actually wrong. A large number of patients had made mathematical errors when manually calculating insulin doses. These patients were under close supervision during the study, so the figures in real life must be even worse, Ziegler speculated. It is not easy for people with diabetes to constantly juggle the numbers in their head. Perhaps this is why something like the bolus advisor is such a welcome addition to diabetes management.

The Proven Benefits of Bolus Calculation in People with Diabetes—The BolusCal Prolongation Study

Signe Schmidt, Hvidovre, Denmark

Signe Schmidt and her colleagues at Hvidovre Hospital were the first to conduct an investigator-initiated clinical study to evaluate the effects of the Accu-Chek Aviva Expert system in clinical practice, which they called the BolusCal Study. Here she reported results from selected subgroups of the BolusCal study population.

The BolusCal Study was a 16-week trial where the effect of the automated bolus advisor implemented in the Accu-Chek Aviva Expert system was used in poorly controlled people with type 1 diabetes.⁴⁸ Forty-three people with diabetes using MDI therapy were taught carbohydrate counting first and were then randomized into either using the Accu-Chek Aviva Expert bolus advisor or trained to mentally calculate insulin doses. Subjects had CGM testing at baseline and at the end of the study. Assessment of satisfaction with treatment was done using the standard Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Happy customers: results

Glycemic control (HbA1c) improved significantly from baseline in both study groups. The drop in HbA1c was comparable between the two groups. The difference in change in HbA1c between the two groups was insignificant. Specifically, CGM data showed that patients using the bolus advisor had spent less time in the hypoglycemic range (<70 mg/dL).

The most striking difference reported between the two groups was not metabolic results, however. It was the patients' reception to the treatment. The DTSQ score was significantly higher in the group using the Accu-Chek Aviva Expert system, indicating these patients were much happier with the treatment offered than was the case with the control group. Treatment satisfaction is an important clinical issue and corresponds to recent emphasis on patient empowerment

and personal satisfaction. Schmidt indicated that treatment satisfaction would ensure better adherence to therapy.

A twist at the end

Schmidt and her colleagues did not terminate studying the patients after the end of the BolusCal study at 16 weeks. They continued to follow up patients at routine clinical appointment for a total of 52 weeks. This became known as the BolusCal Pro(longation) study. The original bolus advisor group continued to use the Accu-Chek Aviva Expert system and to make progressive improvement in the DTSQ. HbA1c levels at 52 weeks remained significantly better than those at baseline in both intervention groups.

Schmidt completed her presentation with random comments made by patients on their experience with the Accu-Chek Aviva Expert system. One quote that particularly caught everyone's attention was: "It has become an integrated part of taking insulin. BG-measurement is now a tool—not a snitch!"

Successful Implementation of Bolus Calculation in Diabetes Management Guidelines and Training Programs—The Danish Example

Kirsten Nørgaard, Hvidovre, Denmark

Denmark before 2010

Denmark, a small but modern and prosperous country in northern Europe, boasts a long and successful tradition in diabetes care and therapy. Denmark has one of the highest incidences of type 1 diabetes in the world. The country is the base of a world-leading manufacturer of insulin therapy. Yet, according to Kirsten Nørgaard, the country is a latecomer to insulin pump therapy and the implementation of carbohydrate counting. Apparently, Denmark had no treatment guidelines for type 1 diabetes until 2010.

These introductory remarks by Nørgaard took many in the audience by surprise. However, the scene has dramatically changed since 2010 because of the diligent work of Nørgaard and her colleagues. Her motto "we can change habits" proved effective and seems to have brought in the right results.

Changing old habits

Nørgaard wanted to outline three events or activities that seemed to have contributed to successful implementation of the bolus calculation concept in Denmark.

The first activity is the release of the new Danish Treatment Guidelines for type 1 diabetes in 2010. For the first time, clear reference was made to carb-counting, especially in the aftermath of the positive results of the BolusCal studies. Several new statements with relevant implications to carb-counting were included in the new guidelines: (1) "the focus of insulin advice should be related to food and physical activity," (2) "carb-counting and estimation is recommended," "insulin should be matched to the carbs," etc.

Carb-counting finally won recognition in the treatment of type 1 diabetes in Denmark, and Nørgaard and her colleagues now had to change old practices and introduce the new concept to the wider community across the country. Nørgaard pursued this in two ways:

1. Prevailing apathy and lack of experience with bolus calculation by healthcare workers needed to be changed, Nørgaard reasoned. So, she set up national courses for bolus calculation in MDI-treated people at the Hvidovre Hospital. Participants included physicians, nurses, and dieticians from around the country. Three hundred healthcare members have been trained so far, with ambitious plans underway to take the course beyond the borders of Denmark.
2. Nørgaard turned her attention to educating people with diabetes on bolus calculation (both manually and with the Accu-Chek Aviva Expert system). Patient training courses have been set up at the Hvidovre Hospital. Because of issues of time, cost, and logistics, the course is approximately 3½ h long. The contents of the course are based on the successful experience drawn from the BolusCal Study. The course is now popular and replicated elsewhere in Denmark.

Nørgaard made an important and practical point about patient selection for the advanced bolus calculation course. She remarked that not every patient on MDI therapy is suitable for training in bolus calculation. Patients must:

- have a real wish to participate.
- have time and energy to be involved.
- be prepared to measure at least four times a day (i.e., do SMBG).
- accept bringing work sheets to ALL visits.
- accept using only one meter.

Nørgaard reflected on the results of routine bolus calculation training at her own clinical practice. She reported that at 6 months following training, patients had a significant and appreciable reduction in HbA1c from the baseline (8.1% vs. 7.5%, $P < 0.001$) with only a 9% dropout rate for the patients studied. Nørgaard seemed very pleased with the results.

The successful experience of Nørgaard and her team in Denmark makes the statement “old habits die hard” false as she shows that changes can be made for the better, at least in Denmark anyway.

Diabetes Management in a Connected World

Dan Kane, Roche Diabetes Care, Indianapolis, Indiana

An outsider's view

Dan Kane introduced himself as being neither a diabetes specialist nor a research scientist. He has worked in the diabetes field for years, and his views on diabetes management proved to be refreshing and clinically important. He unveiled an interesting new initiative developed to improve diabetes management through effective connectivity.

Kane described diabetes management as being made up of three distinct and separate worlds, each of which has its own opportunities and limitations:

1. Patients' realities
 - Diabetes is on the increase globally.
 - Glycemic control remains poor and unacceptable for many patients.
 - Treatment outcome is dependent on the degree of engagement and motivation shown by the patient.

Yet, for individual patients “every act of self-management is a major intrusion on their daily living,” Kane said.

2. Health providers' realities
 - Shortage and lack of interest in diabetes as a specialty among physicians and medical school graduates.
 - Limited physician's time despite the fact that diabetes is not a simple medical disorder but actually a complete way of life for patients.
3. Business realities
 - Escalating costs
 - Increasing reimbursement constraints

The fragmented world of diabetes as it currently stands is not good for diabetes management, Kane declared. Could we try to *connect* everything together and have everyone on board?

A new connected system

Kane reminded the audience of the exciting technological revolution taking place in all aspects of life around us (e.g., Internet banking, online shopping, entertainment, etc.). The central idea is the ability to successfully interconnect to different parties and networks.

Kane introduced a new system in development as a technology-based initiative designed to bring together the different worlds of diabetes with a real-time diabetes management support system. Kane and his team are creating a web or a cloud that can encompass the different parts of diabetes care with a free and automatic flow of information.

“Our first innovation comes to you very soon,” Kane revealed. It is “a meter that connects wirelessly to blue tooth but also offers USB connectivity if needed.” Another invention is a bolus advisor connectable to the mobile phone. Web portal connectivity will also be made easier and user-friendly.

Kane seems to be building up a new diabetes platform “to bring connectivity, people and data together and let the information flow.” These new innovations are the way the diabetic management is heading.

A New Tool to Improve the Interaction Between Physicians and People with Diabetes

Bernhard Landers, Mayen, Germany

Another routine visit to the doctor

Consultation time at the diabetes clinic can be difficult and frustrating for both patient and physician. It can be unproductive because of limited clinic time, important issues not prioritized beforehand (which leads the patient–doctor dialog to a dead end), or disintegration into a futile discussion. For most people with diabetes, a routine visit to the doctor is just “going through the motions.” This is not acceptable, especially in light of the recent calls for patient empowerment and personalized diabetes management. How can we deliver a brief, focused, and well-structured consultation where patients voice their concerns and propose some solutions? Bernhard Landers thinks he has the answer; it is called NOTOS.

All done in 15 min

NOTOS is a questionnaire that the patient gets to fill out while in the waiting room before seeing the doctor. The questionnaire gives the patient an opportunity to self-reflect and define talking points for discussion with the doctor, ensuring the visitation is structured around patient needs and expectations. The questionnaire is electronic on a tablet PC and has graphics with scales, pictures, and traffic lights to enable quick and easy completion. The questionnaire includes topics such as quality of life, social environment, communication, and nutrition. A report is automatically generated and relayed to the doctor's office and forms the basis of the consultation. The doctor can identify the issues of concern to the patient, and an action plan is jointly developed. Achievable goals are subsequently set, and relevant information is stored for future reference. A complete report including the agreed-on goals is handed out to the patient to serve as a reminder.

The questionnaire is not restrictive in nature and allows a considerable degree of flexibility. Not all topics in the questionnaire have to be answered by the patient. By the same token, the doctor can decide to add or omit topics to the questionnaire as clinically relevant for each patient.

With a large diabetes practice to cater for, Landers has found NOTOS a helpful tool in his daily practice. He found that the doctor is getting closer to his patients, treatment is more individualized, and time and resources at the clinic are efficiently spent. "Making your patient your friend" is the best strategy, Landers concluded.

The "Diabetes Tsunami" in Asia—Screening and Management of Postprandial Hyperglycemia as an Option to Prevent Cardiovascular Disease

Manoj Chadha, Mumbai, India

Manoj Chadha offered two main messages to the audience: (1) Diabetes is highly prevalent in Asia and is clinically different from that seen in the West. (2) Postprandial hyperglycemia (PPH) is important for successful diabetes management.

Rising tide

Asia seems to be the epic center of the current diabetes pandemic. Over 90 million people in China and 60 million in India have diabetes. The problem is compounded by the following: (1) A large proportion of the Asian population has either undiagnosed diabetes or prediabetes. (2) Government expenditure per patient is very small in many Asian countries, leading to higher rates of complications and deaths. (3) Asians tend to develop diabetes at a younger age and complications develop one decade earlier than in their white counterparts.

Asian brand of diabetes

Chadha listed some of the characteristics and risk factors associated with diabetes in Asia:

- Asians have a lower threshold for conventional risk factors for diabetes—diabetes develops at a younger age and lower BMI.
- Asians with prediabetes tend to progress to overt disease at a faster rate than observed in the white population.

- Pathogenically, lean East Asians (e.g., Japanese, Koreans) have insulin deficiency as the dominant cause of type 2 diabetes. This has clinical implications when deciding the choice of therapy to use, Chadha said.

PPH

Fasting glucose and HbA1c levels have served as the main parameters used for the assessment of metabolic control. The importance of PPH has only been recently recognized.

Chadha showed several lines of evidence on the significance of PPH:

- PPH is the first indication that glucose homeostasis is deteriorating.⁴⁹
- The work of Wang et al.⁵⁰ performed on type 2 Asian diabetes patients: Using the CGM technique, the group reported PPH contributed predominantly (70%) to the glycemic load in well-controlled patients (HbA1c <7.5%) and contributed equally to that of fasting hyperglycemia in moderately or poorly controlled patients (HbA1c 7.5–10%).
- Chadha presented a long list of studies linking PPH with adverse cardiovascular outcome. He also stressed that there is no cutoff value for this association.

Monitoring and treatment of PPH

Irrespective of the SMBG monitoring profile used, Chadha stressed, the idea of testing is to empower people with diabetes to be actively involved in the management of their disease. Chadha also indicated that patients should be taught on how to take initiative based on SMBG results (e.g., adjust insulin dose) and not merely record glucose data.

Chadha described medications that preferentially target PPH as including α -glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 analogs.

Chadha made some observations about the use of insulin therapy in people with type 2 diabetes. First, insulin therapy is often delayed in the course of the disease. According to Chadha, the average patient would have had an HbA1c level above 7% for at least 10 years before insulin therapy is actually initiated. Second, using high ratio premixed insulins is important: these insulins have a larger content of the rapid-acting insulin (50–70%) and would be more effective in controlling postprandial glycemic peaks. Chadha showed data from two recent studies demonstrating clear benefits of high ratio premixed insulins on postprandial glucose profile and overall metabolic control in people with type 2 diabetes.^{51,52}

Keynote Lecture: The Selfish Brain—Conflicting Interests Between Brain and Body Can Help to Explain Why Diets Often Fail

Achim Peters, Luebeck, Germany

We were taught in medical school that obesity is a serious medical condition associated with poor cardiometabolic outcome. There is plenty of scientific data supporting adverse effects of obesity.

Achim Peters presented a different view on obesity, positioning it as an adaptive physiologic response to a state of

chronic stress and thereby offering a survival advantage to the individual.

Stress breeds fat

According to Peters, factors commonly associated with obesity such as consumption of unhealthy foods, lack of will power, or addiction to sugar have nothing to do with the etiology of obesity. The evidence for that, he argued, was either absent or at best conflicting. In fact, stress seems to be the primary trigger factor to the development of obesity. Exposure to stress or unsafe environment (e.g., poverty, demanding work, unhappy relationship) is not without consequences. There is apparently a heavy health price tag attached to stress (e.g., ischemic heart disease). How individuals react to stress decides the outcome: some individuals are genetically susceptible to adapting (habituate) to stress through increasing body weight. By going obese, these individuals can “absorb the shock” of stress and therefore avert its long-term health consequences. By contrast, individuals who fail to physiologically adapt to stress (i.e., staying slim) and continue with stress unabated will ultimately develop the known health-related effects of chronic stress, including cardiovascular disease.

The selfish brain

The concept proposed by Peters describes the natural characteristic of the brain to cover its own energy requirements with the highest priority when regulating energy fluxes in the body.⁵³ An intrinsic “brain pull” mechanism ensures energy is offered first to the brain at the expense of the rest of the body. This mechanism is driven to a large extent by stress (sympathetic) stimuli. If this “brain pull” mechanism is in some way compromised or interrupted (e.g., in an effort to adapt to stress), the brain demands more energy from the environment to sustain brain energy requirements. The brain eventually gets what it wants, and any surplus of energy becomes deposited in the body as extra weight leading to obesity.

Type A and type B reactions

Peters described two types of reactions on recurrent or permanent stress. First, there are type A individuals, being typically nonadaptive to stress. Such individuals may have a low BMI but in response to stress tend to develop visceral fat and raised serum cortisol, both features representing serious risk factors for cardiometabolic disease. By contrast, type B individuals adapt well to stress through increasing weight (mainly around the hip region) and therefore avoid medical disorders associated with chronic stress. Despite being obese, these individuals tend to live longer than their slim type A personality counterparts, stated Peters.

Dieting is the wrong recipe

If obesity is such a natural and successful adaptive response by the body to stress, then it is physiologically wrong to attempt to reverse it by dieting, Peters concluded. His interpretation was supported by the recent findings from the LOOK AHEAD trial, demonstrating that weight reduction by dieting and exercise did not alter cardiovascular mortality. The most effective way to tackle obesity is to remove the

underlying cause of stress. He reported the outcome of a randomized controlled experiment whereby a group of families were removed from a poverty- and crime-stricken region and taken to live in a safer and less stressful environment. After years of follow-up, the intervention group (stress minimized) had much lower rates of obesity and metabolic disease than those who stayed behind in stressful living conditions.

Abbreviations

BG, blood glucose; BIPM, Bureau International des Poids et Mesures; BMI, body mass index; CE, Conformité Européenne; CGM, continuous glucose monitoring; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HbA_{1c}, glycated hemoglobin; I:CHO, insulin to carbohydrate ratio; ID-GC/MS, isotope dilution-gas chromatography mass spectrometry; ISF, insulin sensitivity factor; ISO, International Organization for Standardization; LGS, low glucose suspend; MARD, mean absolute relative difference; MCII, mental contrasting with implementation intention; MDI, multiple daily injections; PPH, postprandial hyperglycemia; SMBG, self-monitoring of blood glucose; SRM, standard reference material.

Acknowledgments

We thank all the presenters for their contributions.

Author Disclosure Statement

C.S. and R.H. are employees of Roche Diagnostics GmbH. A.A. declares no competing interests exist.

References

1. American Diabetes Association: Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013;36:1033–1046.
2. Wood JR, Miller KM, Maahs DM, Beck RW, Dimeglio LA, Libman IM, Quinn M, Tamborlane WV, Woerner SE; T1D Exchange Clinic Network: Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care* 2013;36:2035–2037.
3. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD: Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010;375:481–489.
4. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AM, Pei H, Bode B; BEGIN Basal-Bolus Type 1 Trial Investigators: Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1489–1497.
5. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, Rosenstock J, Endahl LA, Francisco AM, Hollander P; NN1250-3582 (BEGIN BB T2D) Trial Investigators: Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1498–1507.

6. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, Rodriguez H, Simmons JH, Hirsch IB; T1D Exchange Clinic Network: Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c in T1D Exchange Clinic Registry participants. *Diabetes Care* 2013;36:2009–2014.
7. Garg S, Beatson C, Reed K, Flack F: Use of mobile technology in type 1 diabetes: the REMOTE-T1D Study [poster 2545]. *Diabetes* 2013;62(Suppl 1):A646.
8. Pickup JC, Freeman SC, Sutton AJ: Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self-monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:d3805.
9. Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM: Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care* 2012;35:32–38.
10. Hammond P, Liebl A, Grunder S: International survey of insulin pump users: impact of continuous subcutaneous insulin infusion therapy on glucose control and quality of life. *Prim Care Diabetes* 2007;1:143–146.
11. Pickup JC, Sutton AJ: Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774.
12. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailley G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA; STAR 3 Study Group: Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311–320.
13. Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR: Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther* 2012;14:205–209.
14. Freckmann G, Pleus S, Link M, Zschornack E, Kloetzer HM, Haug C: Performance evaluation of three continuous glucose monitoring systems: comparison of six sensors per subject in parallel. *J Diabetes Sci Technol* 2013;7:842–853.
15. Zschornack E, Schmid C, Pleus S, Link M, Klotzer HM, Obermaier K, Schoemaker M, Strasser M, Frisch G, Schmelzeisen-Redeker G, Haug C, Freckmann G: Evaluation of the performance of a novel system for continuous glucose monitoring. *J Diabetes Sci Technol* 2013;7:815–823.
16. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER: A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci Transl Med* 2010;2:27ra27.
17. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER: Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. *Diabetes Care* 2012;35:2148–2155.
18. The InterAct Consortium: Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. *Diabetologia* 2013;56:1520–1530.
19. Basu S, Yoffe P, Hills N, Lustig RH: The relationship of sugar to population-level diabetes prevalence: an econometric analysis of repeated cross-sectional data. *PLoS One* 2013;8:e57873.
20. Bremer AA, Mietus-Snyder M, Lustig RH: Towards a unifying hypothesis of metabolic syndrome. *Pediatrics* 2012;129:557–570.
21. Liebl A, Hoogma R, Renard E, Geelhoed-Duijvestijn PH, Klein E, Diglas J, Kessler L, Melki V, Diem P, Brun JM, Schaepeynck-Bélicar P, Frei T; European DiaPort Study Group: A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of intra-peritoneal compared with subcutaneous insulin infusion. *Diabetes Obes Metab* 2009;11:1001–1008.
22. Barnard K, Parkin C, Young A, Ashraf M: Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. *J Diabetes Sci Technol* 2012;6:144–149.
23. Boyd JC, Bruns DE: Quality specifications for glucose meters: assessment by simulation modeling of errors in insulin dose. *Clin Chem* 2001;47:209–214.
24. Karon BS, Boyd JC, Klee GG: Glucose meter performance criteria for tight glycemic control estimated by simulation modeling. *Clin Chem* 2010;56:1091–1097.
25. Breton MD, Kovatchev BP: Impact of blood glucose self-monitoring errors on glucose variability, risk for hypoglycemia, and average glucose control in type 1 diabetes: an in silico study. *J Diabetes Sci Technol* 2010;4:562–570.
26. Boyd JC, Bruns DE: Monte Carlo simulation in establishing analytical quality requirements for clinical laboratory tests meeting clinical needs. *Methods Enzymol* 2009;467:411–433.
27. Thorpe GH: Assessing the quality of publications evaluating the accuracy of blood glucose monitoring systems. *Diabetes Technol Ther* 2013;15:253–259.
28. Freckmann G, Schmid C, Baumstark A, Pleus S, Link M, Haug C: System accuracy evaluation of 43 blood glucose monitoring systems for self-monitoring of blood glucose according to DIN EN ISO 15197. *J Diabetes Sci Technol* 2012;6:1060–1075.
29. Baumstark A, Pleus S, Schmid C, Link M, Haug C, Freckmann G: Lot-to-lot variability of test strips and accuracy assessments of systems for self-monitoring of blood glucose according to ISO 15197. *J Diabetes Sci Technol* 2012;6:1076–1086.
30. Brazg RL, Klaff LJ, Parkin CG: Performance variability of seven commonly used self-monitoring of blood glucose systems: clinical considerations for patients and providers. *J Diabetes Sci Technol* 2013;7:144–152.
31. Ceriello A, Barkai L, Christiansen JS, Czupryniak L, Gomis R, Harno K, Kulzer B, Ludvigsson J, Némethyová Z, Owens D, Schnell O, Tankova T, Taskinen MR, Vergès B, Weitgasser R, Wens J: Diabetes as a case study of chronic disease management with a personalized approach: the role of a structured feedback loop. *Diabetes Res Clin Pract* 2012;98:5–10.
32. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, Petersen B, Schweitzer M, Wagner RS: Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. *Diabetes Care* 2011;34:262–267.
33. Kempf K, Tankova T, Martin S: ROSSO-in-praxi-international: long-term effects of self-monitoring of blood glucose on glucometabolic control in patients with type 2 diabetes mellitus not treated with insulin. *Diabetes Technol Ther* 2013;15:89–96.
34. Weissmann J, Mueller A, Pralle K, Ruessmann H, Gregersen B, Messinger D, Amann-Zalán I: Informationsmanagement verbessert signifikant die glykämische Stoffwechseleinstellung bei Typ-2-Diabetes: Ergebnisse der multizentrischen, nicht-interventionellen VISION Studie. *Diabetol Stoffwechsel* 2012;7:P_112. doi: 10.1055/s-0032-1314609.

35. Schütt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R, Mayer I, Rosenbauer J, Wagner C, Zimmermann A, Kerner W, Holl RW; DPV Initiative: Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. *Exp Clin Endocrinol Diabetes* 2006;114:384–388.
36. Karter AJ, Ferrara A, Darbinian JA, Ackerson LM, Selby JV: Self-monitoring of blood glucose: language and financial barriers in a managed care population with diabetes. *Diabetes Care* 2000;23:477–483.
37. Mast O, Schmidt U: Using a strip-free system for self-monitoring of blood glucose resulted in increased test frequencies in nonadherent testers on flexible insulin therapy: a user survey [abstract A100]. *J Diabetes Sci Technol* 2010;4:466–469.
38. Oettingen G: Future thought and behavior change. *Eur Rev Soc Psychol* 2012;23:1–63.
39. Gollwitzer PM: Implementation intentions: strong effects of simple plans. *Am Psychol* 1999;54:493–503.
40. Adriaanse MA, Oettingen G, Gollwitzer PM, Hennes EP, de Ridder DTD, de Wit JBF: When planning is not enough: fighting unhealthy snacking habits by mental contrasting with implementation intentions (MCII). *Eur J Soc Psychol* 2010;40:1277–1293.
41. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C: Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? *Diabetes Care* 2005;28:600–606.
42. Bosi E, Scavini M, Ceriello A, Cucinotta D, Tiengo A, Marino R, Bonizzoni E, Giorgino F; the PRISMA Study Group: Intensive structured self-monitoring of blood glucose and glycemic control in noninsulin-treated type 2 diabetes: the PRISMA randomized trial. *Diabetes Care* 2013 June 4 [Epub ahead of print]. doi: 10.2337/dc13-0092.
43. Franciosi M, Lucisano G, Pellegrini F, Cantarello A, Consoli A, Cucco L, Ghidelli R, Sartore G, Sciangula L, Nicolucci A; ROSES Study Group: ROSES: role of self-monitoring of blood glucose and intensive education in patients with type 2 diabetes not receiving insulin. A pilot randomized clinical trial. *Diabet Med* 2011;28:789–796.
44. Durán A, Martín P, Runkle I, Pérez N, Abad R, Fernández M, Del Valle L, Sanz MF, Calle-Pascual AL: Benefits of self-monitoring blood glucose in the management of new-onset type 2 diabetes mellitus: the St Carlos Study, a prospective randomized clinic-based interventional study with parallel groups. *J Diabetes* 2010;2:203–211.
45. Parkin CG, Buskirk A, Hinnen DA, Axel-Schweitzer M: Results that matter: structured vs. unstructured self-monitoring of blood glucose in type 2 diabetes. *Diabetes Res Clin Pract* 2012;97:6–15.
46. Gross TM, Kaye D, King A, Rother C, Juth S: A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. *Diabetes Technol Ther* 2003;5:365–369.
47. Garg SK, Bookout TR, McFann KK, Kelly WC, Beatson C, Ellis SL, Gutin RS, Gottlieb PA: Improved glycemic control in intensively treated adult subjects with type 1 diabetes using insulin guidance software. *Diabetes Technol Ther* 2008;10:369–375.
48. Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, Nørgaard K: Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. *Diabetes Care* 2012;35:984–990.
49. Monnier L, Colette C, Dunseath GJ, Owens DR: The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care* 2007;30:263–269.
50. Wang JS, Tu ST, Lee IT, Lin SD, Lin SY, Su SL, Lee WJ, Sheu WH: Contribution of postprandial glucose to excess hyperglycaemia in Asian type 2 diabetic patients using continuous glucose monitoring. *Diabetes Metab Res Rev* 2011;27:79–84.
51. Clements MR, Tits J, Kinsley BT, Råstam J, Friberg HH, Ligthelm RJ: Improved glycaemic control of thrice-daily biphasic insulin aspart compared with twice-daily biphasic human insulin; a randomized, open-label trial in patients with type 1 or type 2 diabetes. *Diabetes Obes Metab* 2008;10:229–237.
52. Cucinotta D, Smirnova O, Christiansen JS, Kanc K, le Devehat C, Wojciechowska M, López de la Torre M, Liebl A: Three different premixed combinations of biphasic insulin aspart—comparison of the efficacy and safety in a randomized controlled clinical trial in subjects with type 2 diabetes. *Diabetes Obes Metab* 2009;11:700–708.
53. Peters A, Kubera B, Hubold C, Langemann D: The corpulent phenotype—how the brain maximizes survival in stressful environments. *Front Neurosci* 2013;7:47.

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