

Future Directions in Insulin Therapy and Treatment of Diabetes Mellitus: A Critical Comment

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Considerable progress has been made on our way toward optimal treatment of patients with diabetes mellitus (DM), and many insulin therapy strategies are now available for these patients. We will see further improvements in insulin therapy, and there is hope for a cure in the not too distant future. All of these developments, however, depend on the willingness of the health care and economic systems to fund these new advances. The major burden of this disease is the treatment of DM-related late complications, yet an increased investment in the quality of metabolic control can result in a reduced incidence of these complications. The future of new insulin formulations or new types of insulin applications depends very much on the performance of adequate clinical trials to prove the benefits of such innovations. It requires an open discussion involving all relevant parties, including patients, about the types of clinical studies that are required. (*Clinical Cornerstone*. 2007;8[2]:66–74) Copyright © 2007 Excerpta Medica, Inc.

We have come a long way in the treatment of diabetes mellitus (DM)—from impure insulin formulations made from bovine or pork insulin and needles that patients had to sharpen themselves, to a variety of highly purified human insulin formulations, insulin analogues, and insulin pens with extremely sharp, disposable needles (Figure 1). In the following article, I briefly discuss a number of obstacles on our way toward a future with even better therapeutic options for insulin delivery and glucose monitoring. A bright future does exist for the field of DM treatment, but we must act with caution and foresight.

CLINICAL TRIALS AND THE DILEMMA OF EVIDENCE-BASED MEDICINE

Clearly, for physicians, the aim of treatment for patients with DM is to optimize their metabolic control; therefore, he or she must educate patients about the importance of intensified insulin therapy. We should keep in mind, however, that for patients, the goal may be quite different. Their goal might well be simply to live as normal a life as possible, so discretion and ease of use with regard to insulin administration and glucose monitoring

would be of paramount relevance for them. A regimen that is easy to follow and avoids acute metabolic deterioration would be very attractive. Although not all improvements in diagnostic and therapeutic tools result in a decline in glycosylated hemoglobin (A1C) values, they may lead to a better patient quality of life. The current focus of health care and health insurance, however, is very much on improved metabolic control as reflected by reduced A1C levels, a major outcome measure in randomized controlled trials (RCTs). If no improvement with respect to this parameter can be shown, the results may indicate that an intervention has no proven benefit. From a patient's point of view, however, an intervention might offer considerable advantages, but such soft parameters receive little attention in a world dominated by the economic measure of return on investment (ROI). For example, what is the economic benefit, the ROI, of a patient's reduced need for snacks between meals when taking a rapid-acting insulin rather than regular insulin?

Another issue is the relevance that A1C values have in terms of long-term outcomes. We monitor metabolic control by measuring A1C because we have no other viable parameter. The basis for using A1C values to deter-

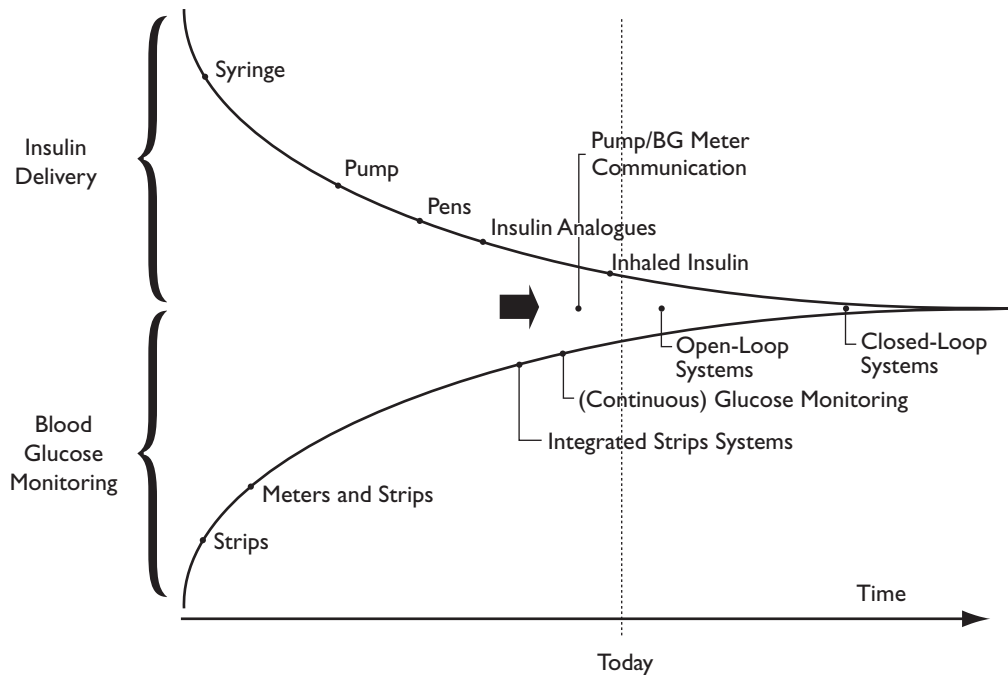


Figure 1. The difficulty of insulin delivery and blood glucose (BG) monitoring has lessened over time and continues to progress toward greater ease of administration and monitoring.

mine the risk of developing DM-related complications comes from the large clinical trials, such as the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, that were done a number of years ago. In almost every article about insulin therapy, you will find a citation for these studies, but we should not forget the limitations of such studies with respect to the type of insulin therapy and the treatment strategies being used at that time. In addition, A1C, as an integrated blood glucose memory, tells us nothing about the swings in glycemia that may occur, nor do capillary blood glucose measurements, which patients perform to make appropriate decisions about the use of intensified insulin therapy. Finally, patients with identical A1C levels might differ considerably with respect to these variations. In view of studies, such as the Verona Diabetes Study,¹ that highlight the importance of such swings on the long-term outcome of patients, especially with respect to cardiovascular mortality, one wonders if A1C is really the ideal parameter to study. Unfortunately, at this time, all large and long-term clinical trials investigating the impact of metabolic control on the development of DM-related complications rely on this parameter. It will not be until new long-term studies investigating the relevance of other parameters to deter-

mine the quality of metabolic control are conducted and the results become available that a shift to a different parameter will occur.

In view of serious attempts by clinical chemists to establish a new standardized method for measuring A1C, which for the first time would allow the comparison of results from different laboratories, a dramatic change in the values we are accustomed to seeing may take place. The new reference values will probably be lower by $\geq 1\%$, and probably by 2% . The question then becomes: what impact will such a change have on patients? While attempting to improve metabolic control, patients may be successful in reducing their A1C values into the range that is currently recommended, but they may not know that the target range was changed and, in fact, was further reduced. Will their attempts at metabolic control, therefore, be considered to have “worsened” because they are targeting the “old” range rather than the “new” range? Such a change in A1C targets will have a tremendous impact on many research projects as well. A1C values currently familiar to patients and physicians could be recalculated to the new standard. One can envision much confusion with the change in A1C targets.

A large study exploring the relationship between blood glucose and A1C is currently under way. Final results of

the study are expected to be presented at the 2007 European Association for the Study of Diabetes and will likely be published soon thereafter. Metabolic control is being monitored with numerous capillary blood glucose measurements taken over several months or by continuous glucose monitoring, and then compared against A1C. The current standardization method for A1C measurement is being used. The premise is that in the future, metabolic control will not be monitored by A1C but by a mean blood glucose number. The hope is that this new value will have more significance for patients.

In the future, we also expect to have the opportunity to continuously monitor glucose profiles. This method should not only help to avoid acute metabolic deterioration completely, but it will also allow patients to evaluate to what extent certain foods, the use of certain therapeutic options, or a given change in treatment produces reductions in postprandial hyper- and hypoglycemic excursions. With continuous glucose monitoring it should also be possible to reduce glycemic variability tremendously.

But if continuous monitoring systems become available, how will we study the potential benefits of new insulin formulations or insulin application techniques in the future? When patients can see their current blood glucose levels displayed on the system at any time and then immediately counteract any swing in glycemia, there probably will be no chance of seeing a difference in A1C levels at the end of a study because differences in the metabolic activity of the study drugs will be balanced by the patients. However, patients may be able to provide information on the need to counteract glycemic excursions with one drug versus another, which, until now, was not an accepted study outcome.

One can also foresee that, with regular use of continuous glucose monitoring systems, interpretation of the outcomes of RCTs may become difficult, and we will need a paradigm shift at this end as well. If such techniques become available, there will be a question of ethics: is it ethical to treat patients in clinical trials over prolonged periods, blinding the display of a device to prevent immediate counteracting by patients to determine the unperturbed effect of the study drug and its comparator and without providing them with a safety net in the form of an early warning system at hypo- or hyperglycemic values?

EVIDENCE-BASED MEDICINE

Before health insurance companies are willing to offer financial reimbursement for new diagnostic or therapeutic options, they request demonstration of a positive cost-benefit ratio. Thus, it is understandable that health insurance companies will require a critical evaluation of the potential benefits of any new diagnostic or therapeutic option (eg, inhaled insulin). In view of the high level of metabolic control that can be achieved with the currently available diagnostic and therapeutic options in well-trained patients, for example, it is not an easy task to show a further improvement in A1C by a new insulin formulation. Within the framework of evidence-based medicine (EBM), the outcome of RCTs with an appropriate study design and performance is regarded as the only reliable approach leading to an unbiased result.

Another more relevant issue is whether patients seen in daily practice are comparable to patients in RCTs that are performed during clinical development. Patients with comorbidities and/or those taking concomitant medications often are not included in such trials, but these are often the types of patients a treating physician actually sees. In addition, patients in daily practice may have a more severe degree of disease and potentially would benefit further from the new drugs or application than patients included in the RCTs.

Although RCTs clearly represent the gold standard for evaluating the effects of a new drug or treatment, we should acknowledge that these studies have limitations. Other approaches (eg, epidemiologic studies) might also have limitations (eg, no randomization), but they could provide a better evaluation of a patient's actual daily experience.

INNOVATIVE STUDY DESIGNS CONTRIBUTE TO OUR KNOWLEDGE

Study designs other than RCTs can contribute important information to help us understand the benefits of a new drug or treatment in more detail. Epidemiologic studies evaluate the impact of drugs or treatment/diagnostic measures under day-to-day conditions by collecting data from a huge number of patient files. Access to such files can be obtained by contacting clinical practices or by analyzing databases that collect these data. With this approach, it is also possible to evaluate hard end points such as DM-related complications, morbidity, and mortality under daily-life conditions—that is, in the unper-

turbed reality. One of the limitations of these studies is that there is no randomization; however, if carefully planned and executed, epidemiologic studies can provide new and meaningful data. The advantages of these studies are that data obtained over a relatively short period can cover a long duration. In addition, there is no need for patient selection, and study effects are avoided. In the framework of EBM, the scientific value of such studies is lower than that of RCTs; however, in view of the additional information these studies can provide, it is important to take them into account. Performance of RCTs focusing on hard end points would require both the inclusion of many patients and a long actual study duration with many patient visits. The cost of such a study would be tremendous. The costs required, in turn, drastically decrease the probability that such long-term studies will ever be performed.

THE CURRENT SITUATION IN GERMANY

There is a fierce ongoing discussion in Germany and Europe about the proven benefits of rapid- and long-acting insulin analogues. In Germany, a review of the published literature conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) did not find any additional benefits for the treatment of patients with type 2 DM with rapid-acting insulin analogues.² According to the criteria of EBM, only a small number of studies could be included in the review. The combined data from these studies found no benefits of rapid-acting insulin analogues compared with regular human insulin with respect to metabolic control and only relatively small advantages with respect to hypoglycemic events. After intense discussion, the reimbursement for rapid-acting insulin analogues for patients with type 2 DM was halted in Germany.

A similar situation occurred with the new inhaled insulin formulation. An IQWiG review of clinical studies of inhaled insulin was also negative; therefore, no reimbursement for inhaled insulin is provided in Germany. The results of an IQWiG review of the benefits of rapid-acting insulin analogues for patients with type 1 DM were published recently as well.³ Similar reviews of long-acting insulin analogues for the treatment of patients with type 1 and type 2 DM are also under way.

After reimbursement for rapid-acting insulin analogues was halted, insulin manufacturing companies offered a discount to health insurance companies that lowered the price for rapid-acting insulin analogues to that of human insulin formulations. Due to this action, rapid-acting

insulin analogues are again reimbursed. But one wonders what the impact of this debate has had on practicing physicians and their patients. A patient may have been using an insulin for quite some time and become comfortable with it and one day is told that, for administrative and economic reasons, he or she must now use a different type of insulin. Then, after a short time, the patient is told that the original insulin formulation can again be prescribed. This constant change in the type of medication being prescribed can confuse patients and have a negative impact on the patient–physician relationship; it can also affect the patients' health. To lessen the confusion, physicians may continue to prescribe the “new” insulin, even if metabolic control was better with the original insulin formulation.

The method used by the IQWiG to select the studies included in their reviews was highly criticized by the pharmaceutical industry and many academics because it appeared that the criteria favored negative studies. A critical question is whether the selected studies were comparable with respect to treatment strategies used. If, for example, basal insulin therapy was optimized in one study with rapid-acting insulin analogues but not in another, is a comparison of the outcome valid? By pooling studies with different treatment strategies, a certain bias can be introduced. Due to the rapid changes in the diagnostic and therapeutic strategies seen in the last few decades, it is not easy to compare the results of a study performed 10 years ago with results from a recent study. Other factors can introduce bias into study results. For example, if patients receive medication at no cost during a study but otherwise would not take the medication because they would have to pay for it themselves, this might influence the results.

Because of the consequences of the IQWiG review of rapid-acting insulin analogues regarding reimbursement, other therapeutic and diagnostic measures for DM care are being carefully observed by other countries. Even in the United States, a reassessment of the proven benefit of rapid-acting insulin analogues has begun. Given the increase in the number of individuals with type 2 DM worldwide and the cost of DM care, this is fully understandable.

WHO WILL FUND NEW CLINICAL TRIALS?

In view of the shortage of clinical trials that are accepted by an institution such as the IQWiG, better long-term studies to confirm the real benefits of a new insulin prod-

uct are of the utmost importance. However, given the number of studies conducted for rapid-acting insulin formulations and novel formulations such as inhaled insulin, one wonders about the risk that all such investments will ultimately fail. Thus, we must demand better clinical trials, but we must also acknowledge that pharmaceutical companies may be reluctant to finance new and probably more expensive studies given the high risk of a negative outcome or that the results of such studies will not be accepted by institutions such as the IQWiG.

If we want high-quality studies with clear-cut outcomes that allow for an exact statement about the cost-benefit ratio of a new diagnostic or therapeutic option, we must agree on how to finance such studies. Typically, new studies are expected to be paid for by the pharmaceutical industry—by the companies researching and developing the new diagnostic or therapeutic option. Yet when a study is paid for by a pharmaceutical company and there is a positive outcome, the results are treated with suspicion. Studies performed by academic institutions are regarded as being of higher value than studies performed by professional organizations funded by the pharmaceutical industry. However, the quality of studies by academic institutions can actually be much lower than that of studies performed by professional organizations.

Performance of clinical trials is highly formalized and controlled. Once a study design is approved and the trial is completed, there is no room for influencing the outcome. This is clearly an improvement compared with the situation before Good Clinical Practice guidelines were implemented. However, in the choice of study design and in the analysis and interpretation of study data, there is room for shifting the results in a certain direction. It is fascinating to see how the results of huge studies presented over the last few years can be interpreted in such different ways by different people and groups.

There is another critical aspect of clinical studies that should be discussed. If appropriate long-term RCTs are initiated today, it will take several years before the results of these studies become available. During that time, however, new developments may occur that will reduce the value of the outcomes of these studies. In addition, a positive outcome in terms of performance or effectiveness may not be accepted for reasons not related to the study results but rather for reasons of cost. In either case, there is a certain risk for the institution that has financed the study that the outcome will not be what was anticipated.

This is not an issue if the institution is a neutral one, such as the government or a health care company, but a commercial company clearly has the hope that the outcome is beneficial to their investment.

Another question is: when should such studies be performed? Until now, companies had to perform a rather well-described set of studies showing the safety and efficacy of a new drug and then apply for drug approval. If more clinical trials with longer study durations are required, this prolongs the time period before the drug can get approval and reduces the time before the patent for the drug expires. To get a good ROI, the company would be forced to increase the price of the drug. During the clinical development of insulin lispro and other insulin analogues over the last 20 years, a number of clinical trials were performed by the pharmaceutical industry in cooperation with academic centers to evaluate the safety and efficacy of these agents in order to achieve market approval (**Figure 2**). Most often, the results of such studies were published in the years *after* the drugs were introduced into the market. Thus, for a physician whose goal is to treat a patient with such drugs, the necessary medical information might not be present when the drug becomes available. If we force the pharmaceutical industry to perform long-term studies before the drugs are approved, we also run into an ethical issue. By this procedure, it might take even longer before new drugs become available that may help patients improve their metabolic control and prevent or delay complications. It is necessary to balance the potential risks and costs of new drugs with such benefits.

If we say the pharmaceutical industry should not pay for such studies in total, who else can finance these studies—at least in part?

THE RULES FOR THE GAME HAVE CHANGED

As stated earlier, in the past, pharmaceutical companies performed RCTs that reported efficacy and safety to get market approval for new agents. Interestingly, it was sufficient for these studies to demonstrate noninferiority to already approved agents. After approval, many studies were performed for marketing purposes but not to prove specific benefits of the new agent. It is therefore not surprising that a critical review of the published literature produces a negative statement. The new situation is that the medical benefit of already approved substances should be

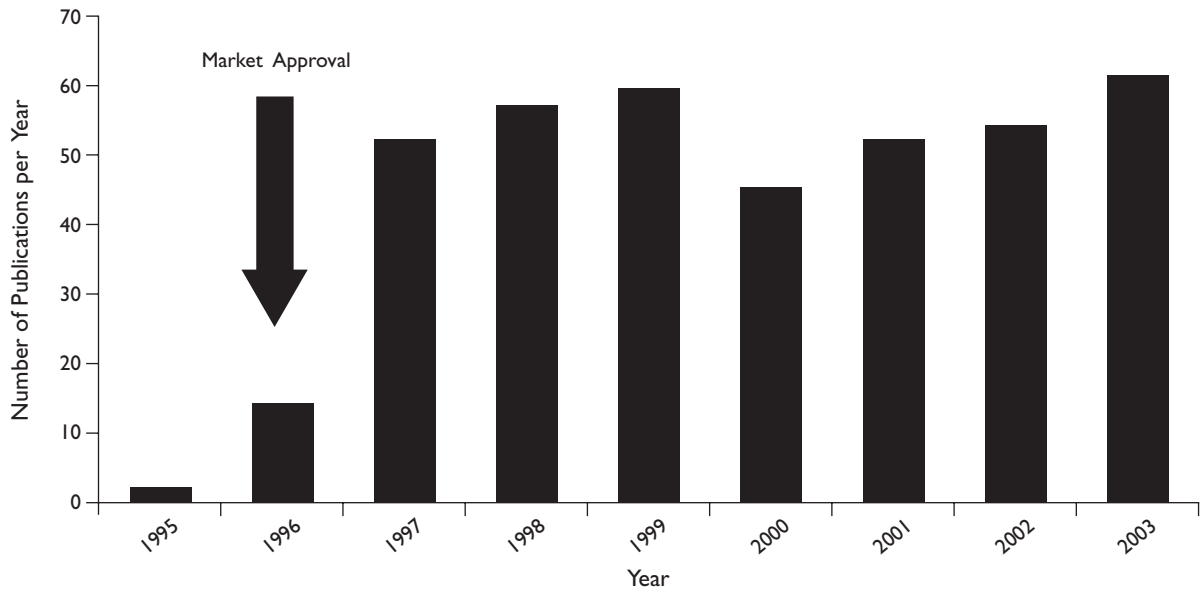


Figure 2. Hundreds of publications discussing insulin lispro were published between 1995 and 2003 during the clinical development of that and other insulin analogue formulations. However, clinical trial results are often published after introduction of the drugs into the market and therefore may not be available to physicians who may want to treat their patients with the new agents.

proven years after entering the market. This change in the rules first astonished and confused pharmaceutical companies. However, they are now forced to perform more appropriate and better designed clinical trials at an earlier stage.

INSULIN: NEW APPROACHES

Is there still a need to improve the currently available insulin formulations? First, we have to acknowledge that the improved pharmacodynamic properties of insulin formulations are not a substitute for improved metabolic control and avoidance of acute metabolic deteriorations. Many other factors must be taken into account to achieve these goals. For example, adequate instruction for patients is probably more important than simply providing improved insulin formulations. Nonetheless, an even faster onset of action and an even flatter profile of action, along with a reduced variability of action, will help in practice. Therefore, while room for further improvement exists, we cannot be sure that more insulin analogues will come to market because of the unpredictable risks for the pharmaceutical companies. These companies will be reluctant to invest heavily in the development of such analogues and other drugs if they cannot be sure that reimbursement will occur.

In recent years, the main focus in the attempt to improve the pharmacodynamic properties of insulin formu-

lations has been on insulin analogues. However, in principle, many more options are available to achieve this goal. Attempts in the past to increase insulin absorption by increasing local blood flow have not led to a product; however, other treatments are currently in clinical development. First, reducing the self-assembling tendency of regular human insulin molecules into hexamers and masking negative charges on the surface of the insulin molecule have been found to produce an onset of action that is even more rapid than that of a rapid-acting insulin analogue.⁴ Another treatment in development is the intradermal injection of regular insulin, which greatly increases the speed of insulin absorption and its onset of action.⁵

Such promising examples show that new approaches are possible. Potentially, different routes of insulin administration (eg, inhaled insulin) might also offer advantages with respect to the achieved metabolic effect. As the example of Biodel Inc shows, even with the most established route of insulin administration—SC injection—unexpected improvements are possible. Biodel, a specialty pharmaceutical company located in Danbury, Connecticut, has developed a very rapid-acting form of SC injectable human insulin for mealtime use in type 1 and type 2 DM.⁶ Because the basic mechanisms of insulin absorption into the skin were not fully understood until recently, there is

probably even more room for improvement. There are many other factors that influence the insulin absorption process that are currently being studied.

IS INSULIN THERAPY CURRENTLY A NO-BRAINER?

SC insulin injection has been the standard DM therapy for nearly 85 years. The relatively small number of presentations about this topic at the important international diabetes meetings, such as the European Association for the Study of Diabetes or the American Diabetes Association, implies that many people believe this is no longer a “hot” topic for scientific and clinical research. However, a renaissance of such research would be beneficial. The invention of insulin analogues and their clinical development has allowed the study of many questions of clinical relevance, but many remain. For example, the impact of factors, such as age, gender, body mass index, site of application, dose on the time–action profiles of the various insulin formulations, and presence of diabetic nephropathy, is still poorly understood. Most likely, such factors lead to clinically relevant differences, which in turn contribute to insufficient insulin therapy. It also appears that many of the younger diabetologists may be lacking the details of insulin therapy.

An important step in a new direction could be a more intense communication between academic sites and insulin manufacturers, which would allow both sides to understand the needs of the other. More specific meetings and symposia—for example, the Diabetes Technology Meeting and the Insulin Congress—provide a good sounding board to discuss the aspects and design of appropriate studies.

Variability of Insulin Action

In daily life, the most disturbing experience for patients with DM is unpredictable blood glucose levels. This results not only in unexpected hypo- or hyperglycemic episodes, but it also hampers achievement of optimal metabolic control. The high variability of insulin action leads to considerable discouragement for patients, which in turn reduces their compliance. They may feel that independent of all their efforts, their blood glucose levels still fluctuate. Thus, variability of insulin action is a significant problem.

Insulin absorption from the SC depot is mainly influenced by local blood flow. Therefore, all factors influ-

encing this flow have a tremendous effect. In addition to an improved time–action profile, another potential benefit of other routes of administration could be reduced variability. As already described, reduced variability may lead to improved patient compliance. This advantage is probably of more relevance for patients than avoidance of the pain associated with SC injection.

Costs

Inhaled insulin is the only alternative route of administration for which at least one product has achieved market approval. The costs, however, are a critical issue. Because of the low biopotency of inhaled insulin (10%–15%), the amount of insulin that has to be applied to achieve a metabolic effect comparable to that of an SC injection must be higher.⁷ Even if the amount of insulin in a given insulin formulation is only a part of the total cost, the price of inhaled insulin is higher than that for other formulations. Given the fact that the metabolic control achieved with inhaled insulin in the RCTs performed thus far is comparable to that of SC insulin,⁷ it is not easy to justify the higher price. However, there are at least some aspects that should be carefully studied before this approach is banned from reimbursement, as is currently the case in Germany. It might be that patients with type 2 DM will start insulin therapy earlier if they do not have to inject the insulin. For many patients, the need to inject insulin is a symbol that they have reached the last stage of their disease. It may also be that inhaling insulin rather than injecting it leads to a more appropriate metabolic effect with respect to timing in overweight and older patients. Appropriate cost–benefit analyses should be performed to clarify these aspects. However, it is not easy to predict the benefits of a new invention when patients have no chance to evaluate these products themselves. In the past, the introduction of insulin pens and blood glucose meters into the market was heavily criticized by diabetologists. Yet patients now regard such developments not simply as gadgets but as devices that help them handle their disease more easily and effectively in daily life. These devices have become part of standard therapy.

What Is the Future of Insulin Injections?

The desire of patients to rid themselves of SC insulin injections is fueling the activities of a number of companies and researchers to develop oral, buccal, transder-

mal, or nasal insulin. In fact, some individuals believe that the successful development of an oral insulin will allow the jump directly from SC insulin therapy to insulin pills and to bypass inhaled insulin altogether. In light of our earlier discussion, however, it is obvious that if such developments do not address clear medical needs and if they are more expensive than the currently established insulin therapies, the health insurance companies will be reluctant to reimburse the cost of such products. At the moment, there are still many innovative approaches and creative ideas in varying stages of development. This may change, however, when it becomes clear that high obstacles have been raised. The only key to overcoming these obstacles is to prove the safety and efficacy of new agents in adequately designed and performed studies. But because these studies are expensive, it is difficult for smaller companies to finance them.

Insulin Pumps

Insulin pumps have become much smaller and more user-friendly in the last few decades. However, despite all the electronic and computer power they entail, no fundamental changes have taken place. Critical questions have been raised about whether all the features built into the recent pumps are really useful. Surprisingly, the number of studies trying to provide answers to such questions is small. For example, the impact of the manner in which meal-related bolus insulin is infused has been poorly studied. Also, only a few studies thus far have investigated whether pumps are an appropriate option for patients with type 2 DM.

A number of companies are actively developing new “smart” insulin pumps; many of them are low-cost systems that would allow discharge after a single use. Such pumps have no catheter but a needle that is inserted automatically when the pump is applied and retracted once the pump is removed. Only one fixed basal insulin infusion rate will be provided; however, this may be adequate for many patients with type 2 DM.

This is an area in which well-designed and well-performed clinical trials are desperately needed to provide evidence.

Sources for Insulin

Today, insulin is manufactured in huge biotechnology plants, the biggest of which can produce tons of insulin per year. These established lines produce insulin that is

of a very high quality; despite this, a number of companies are trying to develop novel and cheaper routes of insulin production.

OUTLOOK FOR THE FUTURE

The insulin market is a growing one, mainly due to the increasing number of patients with type 2 DM. This is, at least in part, also due to the demographic changes we have all seen. The mean age of the population has shifted to older groups, but “Baby Boomers” are becoming more and more predominant among patients being diagnosed with diabetes for the first time. The insulin market might be overwhelmed by the growing number of drugs that improve metabolic control in patients with DM using other methods. Front-runners are the incretin hormones. The first analogue of the endogenously produced and secreted glucagon-like peptide-1 (GLP-1)—the incretin hormone exenatide—is now on the market in the United States. Incretin hormones help to improve patients’ metabolic control while also reducing body weight. Because the effect of these drugs is diminished once blood glucose is in the normoglycemic range, the need to monitor blood glucose by finger-stick checks is also reduced.

Whereas a fixed dose of exenatide must be injected BID into SC tissue, the first drug to reduce the degradation of endogenously secreted GLP-1—sitagliptin—has received market approval in the United States and Europe. This so-called dipeptidyl peptidase (DPP)-IV inhibitor can be taken orally.

DISCUSSION

It is my strong belief that we have made considerable progress in the last few years on our way toward an optimal treatment of patients with DM. Besides the hope that a cure for DM will be possible in the not too far future—whether it is a technical cure by means of an automated pancreas, or a biological cure by stem cells or artificially produced islets—we will see further improvements in insulin therapy.

However, these new options are dependent on the willingness of the health care industry to fund new developments. An increased investment in the quality of metabolic control does pay off in the long run by a reduced incidence of DM-related late complications. The major burden from an economic point of view, as well as from a patient’s point of view, is the treatment of these late complications. If we can prevent or delay the appearance

of these complications by means of a better insulin therapy, something that clearly has to be demonstrated, higher costs can be justified. This, in turn, would fuel the development of new and innovative ideas and would allow them to come to fruition.

CONCLUSIONS

The future of newly developed insulin formulations or new types of insulin applications depends very much on the performance of adequate clinical trials to prove the benefits of such innovations. It requires an open discussion involving all relevant parties, including patients, about which clinical studies are required and how they should be financed.

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REFERENCES

1. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: The Verona Diabetes Study. *Diabetes Care*. 2000;23:45–50.
2. Final report: Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2. Available at: http://www.iqwig.de/download/A05-04_Final_Report_Rapid-acting_insulin_analogues_for_the_treatment_of_diabetes_mellitus_type_2.pdf. Accessed August 9, 2007.
3. Executive summary: Rapid-acting insulin analogues for the treatment of diabetes mellitus type 1. Available at: http://www.iqwig.de/download/A05-02_Executive_Summary_Rapid-acting_insulin_analogues_in_the_treatment_of_diabetes_mellitus_type_1.pdf. Accessed August 9, 2007.
4. Steiner S, Hompesch M, Pohl R, et al. Pharmacodynamic properties of Viaject: A novel rapid-acting regular human insulin. *Diabetologie und Stoffwechsel*. 2006;1(Suppl 1): S93.
5. Pettis RJ, Hompesch M, Kapitza C, et al. Intra-dermal insulin lispro application with a new microneedle delivery system led to a substantially more rapid insulin absorption than subcutaneous injection. *Diabetes*. 2006;55(Suppl 1): A26.
6. Medical News Today: Bidel Inc announces VIAject™ data at oral presentation at the American Diabetes Association Meeting. June 23, 2007. Available at: <http://www.medicalnewstoday.com/articles/75038.pshp>. Accessed August 10, 2007.
7. Heinemann L, Heise T. Current status of the development of inhaled insulin. *Br J Diabetes Vasc Dis*. 2004;4:295–301.