Journal of Diabetes Science and Technology
Volume 6, Issue 4, July 2012
© Diabetes Technology Society

REVIEW ARTICLE

Insulin Infusion Set: The Achilles Heel of Continuous Subcutaneous Insulin Infusion

Lutz Heinemann, Ph.D.,[1] and Lars Krinelke, M.D., Ph.D.[2]

Abstract

Continuous subcutaneous insulin infusion from an insulin pump depends on reliable transfer of the pumped insulin to the subcutaneous insulin depot by means of an insulin infusion set (IIS). Despite their widespread use, the published knowledge about IISs and related issues regarding the impact of placement and wear time on insulin absorption/insulin action is relatively small. We also have to acknowledge that our knowledge is limited with regard to how often patients encounter issues with IISs. Reading pump wearer blogs, for instance, suggests that these are a frequent source of trouble. There are no prospective clinical studies available on current IIS and insulin formulations that provide representative data on the type and frequency of issues with infusion sets. The introduction of new IISs and patch pumps may foster a reassessment of available products and of patient problems related to their use. The aim of this review is to summarize the current knowledge and recommendations about IISs and to highlight potential directions of IIS development in order to make insulin absorption safer and more efficient.

J Diabetes Sci Technol 2012;6(4):954-964

Introduction

Insulin therapy by means of continuous subcutaneous insulin infusion (CSII) is a well-established therapeutic option.[1–6] Since the 1980s, insulin pumps have developed into highly sophisticated infusion devices that provide infusion of different types of insulin boli.[7] The most recent versions of these pumps have also integrated information management and advice functions.

The traditional insulin pump is connected to the patient via thin, soft, and flexible plastic tubing. One end of this tubing is attached to a needle that goes through the skin into the subcutaneous (SC) adipose tissue. The needle is either a steel needle or a soft Teflon catheter, which is inserted at various angles through the skin. The other end of the tubing is connected to the pump's insulin cartridge via a Luer-lock or proprietary connector. Once the set is attached to the skin, insulin is pumped through the infusion set into the SC area to induce a metabolic effect according to the wearer's current needs. Lower infusion rates cover the basal insulin

Author Affiliations: [1]Science & Co, Düsseldorf, Germany; and [2]Roche Diabetes Care AG, Roche, Burgdorf, Switzerland

Abbreviations: (ATBF) adipose tissue blood flow, (AUC) area under curve, (BMI) body mass index, (CSII) continuous subcutaneous insulin infusion, (IIS) insulin infusion set, (LHT) lipohypertrophy, (SC) subcutaneous, (T1DM) type 1 diabetes

Keywords: infusion set, insulin pumps, insulin therapy

Corresponding Author: Lutz Heinemann, Ph.D., Science & Co., Kehler Str. 9, 40468 Düsseldorf, Germany; email address L.Heinemann@science-co.com

requirements, while higher rates (boli) are given to cover prandial insulin requirements and hyperglycemia. Insulin infusion sets (IISs) are available in a variety of different lengths, diameters, connectors, materials, and designs to meet the individual patient requirements.

Another type of insulin pump that has been introduced into the marketplace is the so-called patch pump. The main difference between patch pumps and traditional insulin pumps is that these new pumps—with one exception—have no visible IIS. Typically, these patch pumps have a very short IIS, but it is completely inside the pump housing or within the base part of the modular designed pump.[8] The adhesive that fastens the IIS to the skin is located on the patch pump or on its cradle base. In other words, an IIS is an essential part of each type of insulin pump.

One might think that there are no issues with IIS in view of the relative paucity of published studies; however, an Internet search resulted in numerous hits and shows that this topic is of major concern for patients using insulin pumps. The aim of this review is to summarize the published literature about IISs and related issues. Our focus is on clinical studies published since 2000; although, in older studies, the types of IISs, pumps, and insulin formulation studied are no longer in use. This review may help to initiate a more systematic and scientific approach to IISs to allow safe and efficient insulin therapy with CSII under the various circumstances of normal daily life.

Plethora of Insulin Infusion Sets

A considerable variety of IISs is available to accommodate patients' characteristics and requirements as well the different types of insulin pumps. Many IISs have a standard threaded Luer-lock connection that attaches them to the pumps. Insulin infusion sets can be categorized by:

- **Angle of insertion into the skin**: This angle can be either 90°/perpendicular (straight insertion), which allows the insertion depth to be varied by the use of different needle lengths, or approximately 45° to the skin surface (slanted insertion). In the latter case, the needle lengths range from 12 to 19 mm, and by changing the cannula angle, patients can adjust the penetration depth into the SC tissue.

- **Length of the needle/catheter**: The lengths vary from 4.5 to 19 mm to enable infusion of insulin into different depths of the SC adipose tissue. The purpose for selecting the appropriate needle length is to avoid intramuscular insertion/infusion or traumatizing muscle fascia while the tip is well inside the adipose tissue, thereby guaranteeing optimal conditions for insulin absorption It is advisable that the needle tip is as deep as possible in the SC tissue but not painful.

  So far, the choice of the appropriate needle length for the patient is determined by insertion angle and thickness of SC tissue. The latter varies considerably among patients, depending on many factors.[9] It is undecided whether the selected needle length should be influenced by the type of cannula material used, as the use of a flexible Teflon needle may potentially contribute to cannula kinking or to slipping out from the insertion site during body movements.

- **Cannula material**: Thin steel needles are inserted and remain in the SC tissue during the period of wear. The thicker plastic cannula of a Teflon IIS stays in the skin after its insertion, while a metal mandarin is removed after insertion.

- **Length of the tubing**: Tubing lengths of conventional IISs vary from 30 to 110 cm. The length is selected according to an individual patient's preference as to IIS insertion site.

Other characteristics that allow differentiating between IISs are the material of the integrated adhesive, the option to disconnect the needle/catheter part from the tubing, and the respective location of the potentially available connector (on top of the head's adhesive, or after an approximate 10 cm tubing to form a security loop). In addition, the infusion sets can also be categorized by the need for or availability of an insertion device. Placement of steel needles does not usually require any inserter, whereas for Teflon cannulas, the use of an inserter is recommended. Such inserters can be integrated into patch pumps, connected to the IIS head, or can remain separate, external devices. The inserter helps place the tip of the needle in the SC tissue in a consistent and painless way. The amount of packaging material required for the inserter is remarkable.

Despite the apparent plethora of existing IISs (with a variety of brand names) that aim to address patient specificity and potential problems (e.g., skin irritations or allergic reactions to the adhesive or tubing material), the true number of IIS manufacturers is very limited. Most of

the IISs are produced by a single manufacturer in Denmark. Therefore, one would assume that, in practice, not many significant treatment-related differences exist among the offered IISs. The choice of IIS is very much a matter of a patient's personal preference and experience with which IIS works best for them.

Unfortunately, we were unable to find reliable, unbiased data about which types of IISs are used the most. These data might differ considerably among countries. Data from one insulin pump manufacturer (Roche Diabetes Care AG, data on file) demonstrate regional differences between the preferred types of IISs. In the United States, less than 10% of patients use steel catheters, whereas the majority of patients prefer Teflon infusion sets (approximately 30% angled and 60% perpendicularly inserted). In Europe, Teflon needles are used by the majority of patients as well (approximately 20% angled and 55% perpendicularly inserted). In contrast to the United States, the share of metal cannulas is higher (Europe-wide, approximately 25%) with the highest rate in Germany (approximately 40%). The results have to be interpreted with great caution, as there is a reporting bias associated with such methodological approaches. The differences in using steel or Teflon catheters are surely reflecting the market activities of the pump manufacturers. However, to our knowledge, no other data from adequately designed and powered clinical studies and registries are available.

Body Sites and Needle Length

An IIS can be placed in several anatomical places based on personal preference. Anatomical regions recommended for insulin delivery either by injection or insulin pump include the arm, abdomen, thigh, and buttocks.[10–12] Predominantly, the abdomen is used as the insertion site for the IIS since insertion here is convenient and comfortable. Nevertheless, no studies on the impact of using different anatomical regions for insulin pump therapy were retrieved by the literature search performed on this subject. Thus, information outlined here is based on studies using SC insulin injection for the corresponding anatomical regions. General conditions for absorption and glucose lowering action of insulin after SC injection and infusion, respectively, are comparable despite the fact that the time required to build up an insulin depot may differ significantly.[13]

Subcutaneously administered regular insulin is absorbed at different rates by the different anatomical regions that are used: most rapidly by the abdomen, next most rapidly by the arms, and most slowly by the thighs and buttocks.[14–20] Even for a particular region, such as the abdomen, absorption of subcutaneously injected human insulin can vary to a significant extent.[21,22] Faster insulin absorption is associated with an increased peak plasma concentration and a shortened time to peak.[15] Likewise, postprandial rise in plasma glucose concentration varies inversely with the rate of insulin absorption from different anatomical regions and was 30 to 50 mg/dl less after abdominal injection than after leg injection.[16] Bantle and colleagues[18] examined the effect of differences in absorption of regular insulin from abdomen and thigh in diabetes subjects with plasma glucose and serum free insulin as main outcomes. The study authors concluded that regular insulin injected into SC fat tissue of the abdomen causes larger reductions in plasma glucose than if injected into the thigh. Changing the injection site from the abdomen to the thigh had an effect equivalent to reducing the dose administered. Also, if the skin of a given patient is warm, e.g., in the abdominal region, but cold on the arm, injection in either of the two sites might result in clinically meaningful differences in insulin absorption (due to differences in local blood flow), especially in people with low insulin requirements, such as children. However, clinicians are not sure about the practical impact such site-to-site differences have in daily practice. In line with this, a study using rapid-acting insulin aspart found no statistically significant differences in its absorption and glucose-lowering action depending on the injection site.[19] The duration of the glucose-lowering effect of insulin aspart was significantly shorter after abdominal injections than after injections into the deltoid muscle or thigh. Similar observations were made for insulin lispro.[23] The study authors concluded that the consistency in insulin lispro response by abdominal and extremity injection sites allows more potential sites for SC injection with an assured rapid response.

Site selection influences needle length selection, taking into account the factors mentioned earlier about SC adipose tissue thickness. Typically, for an abdomen insertion site, the cannula length for a given patient varies with age and SC tissue thickness. European recommendations have suggested 6 mm for infants, 8 mm for a child, 10 mm for an adult, and 12 mm for obese adults with a straight needle vs 13 or 19 mm for the slanted needles. According to American Association of Diabetes Educators, 6 mm 90° sets and 13 mm 30–45° angled IISs are appropriate for most patients (*http://www.diabeteseducator.org/export/sites/aade/_resources/pdf/research/12-30-11-AADE_Insulin_*

WhitePaper_Print.pdf). Only patients with high body mass index (BMI), large insulin boli (≥25 units), or basal rates ≥2.5 units/h, as well as patients who have experienced lipohypertrophy (LHT) or difficulties with respect to a reliable SC insulin delivery, may be candidates for longer catheters.

Interestingly, there is a relation between the site used for insulin administration and the risk of exercise-related hypoglycemia.[24] Accordingly, leg exercise accelerates absorption of insulin in the thigh during the post-exercise recovery period but does not affect nor even slightly inhibit insulin absorption from its depot in the upper arm and abdomen, respectively.[25]

Disinfection of the Infusion Site

It is usually recommended that the SC infusion site be adequately disinfected prior to needle insertion. With insulin infusion, the risk of local bacterial infection is higher than with SC injection.[26] The IIS remains on the same site for several days; beneath the tape used to affix the needle at the insertion site, it is warm and humid. This provides ideal conditions for bacteria growth.

In a nationwide pediatric surveillance of IIS in Germany and Austria, 83% of the patients reported that they disinfect the skin regularly before they insert the IIS.[27] These patients had a skin complication rate of 72%. The complication rate of the 9% of patients who reported that they never disinfect was only 60%. The study authors concluded that there was no benefit in disinfection. Such recommendations have to be taken with caution, as these are self-selected groups of patients.

In a large international survey among 14,012 pump users, 74.4% of the patients reported that they disinfect the insertion area.[28] Those patients reported the occurrence of skin problems on a regular basis at a rate of 41.5%. Patients who did not disinfect their skin (25.6%) prior to IIS placement observed skin complications at a rate of 42.6% (not significant). These numbers may reflect the existence of a patient group that is not prone to the development of infusion site complications. However, there might be a clear need in other patients to disinfect; this has to be verified in a prospective clinical study. An alternate explanation for higher skin infection rates despite disinfection is the inadequate use of alcohol swabs. Many patients (and care givers) use a circular motion, thus swiping bacteria back into the area that is supposed to be disinfected.

Frequency of Insulin Infusion Set Replacement

The manufacturers of IISs and insulin formulations used in insulin pumps recommend changing IISs and infusion site every 2–3 days in order to avoid skin and infusion problems. However, in reality, these infusion site-related recommendations are based only on reports derived from anecdotal data sets about use of the IIS in daily practice.[29–36] Thorough investigations providing a scientific rationale for depicting a safe interval for the changes are still lacking to date. Kerr and colleagues[34] demonstrated that early IIS occlusions (within 3 days) are rare and independent of the type of rapid acting insulin analog studied. These authors have recommended that the IIS should be replaced within 3 days irrespective of the insulin used. Nevertheless, many patients report that, in practice, they often use their IIS for several days or even longer without any issues.

Only two studies were published that evaluate how often patients change their IIS: in a Swedish survey about patient management with 90 patients, the interval in which soft cannula IISs were changed ranged from 2 to 10 days (with a mean of 4.8 days) and for metal needles 1.5 to 7.5 days (3.8 days);[37] in an international survey[28] performed in 2001 and 2002, 76% of patients on CSII reported changing their IIS every 2–3 days, 5% changed it every day, and only 19% reported using the IIS for longer time periods. Patients who were using metal IISs exchanged them on average every 2.7 days (with a large range from 1 to 20 days). The user of Teflon sets replaced them every 3.1 days (also with a large range from 1 to 30 days).

In practice, many patients still change the line less frequently than reported and often do not change the IIS until their blood glucose levels start to rise despite appropriate insulin dosing or until the insulin cartridge in the pump is empty. Another question is if they change the infusion site even when the cartridge is not empty. Not changing the infusion site increases the risk of LHT alterations of the SC tissue, and overly frequent use of the same infusion site (more often than every 10 days) may induce skin infections.

Insulin Infusion Set-Related Issues

When patients on CSII decide to discontinue insulin pump therapy, one of the main reasons is issues with the IIS.[38–40] One can regard the IIS as the Achilles heel of CSII.

There is a broad variety of issues with the IIS; however, they can be separated into these main areas:

- Patients' biological/medical specificity (e.g., skin hypersensitivity to certain materials, insufficient binding of a particular adhesive brand on the skin), technical problems of the IIS (e.g., design or material issues)

- Handling issues (e.g., poor insertion technique, overly long duration of IIS use, leaking IIS, poor IIS design)

Skin Problems

Several studies were published in the 1980s and 1990s reporting the prevalence of infected infusion sites: one comparative study of 161 patients treated with CSII and 165 patients with conventional insulin therapy,[41] one retrospective study,[42] an observational study of 177 patients for a mean duration of 36 months,[43] and self-reported data of 116 patients for a total of 518 patient years.[44] Between 30% and 36% of pump users reported infected sites or inflammation.[41,43] However, these data are difficult to interpret; more recent data are needed.

Skin problems can show up as a result of acute reaction to the IIS or its long-term usage at the same site: redness, pruritus, pain, scars, or LHT. Such irritation can be the result of the insertion *per se* and/or the plaster used. In rare cases, inflammation or even infection was observed with an IIS—most often these reactions were mild and did not require antibiotic treatment, nevertheless, occasional development of an abscess was observed.[41,45] In single cases, serious systemic complications have been attributed to IIS-related infections; these include a case of acute bacterial endocarditis[46] and a case of toxic-shock syndrome.[47] However, it has to be highlighted that both cases were reported nearly 30 years ago.

Bacterial infusion site infection and contact dermatitis caused by IIS adhesive, although rare, can arise in the context of CSII therapy. Infusion site infections were reported to be caused most often by Staphylococcus bacteria that have seeded from the skin flora, but other pathogens (e.g., Streptococcus) may also be involved.[48] Certain factors, such as hairy skin, profuse perspiration, atopic skin inflammation, and poor metabolic control increase the risk of infection.[45] The high frequency of infections reported in early pump studies might have been a consequence of inadequate hygienic precautions when inserting the IIS and too infrequent change of the IIS. A patient that is a Staphylococcus carrier should change his IIS more often to avoid infection, but it is not clear that those not prone to infection need to do this as well. In 1983, the Center for Disease Control published a case study of an 11-year-old girl who often did not change the IIS for up to 10 days, resulting in a Staphylococcus aureus abscess at the insertion site and toxic shock syndrome.[47] Later studies concluded that the risk of acute cutaneous complications increases with the indwelling time of the IIS, mainly when exceeding 48 h.[49,50]

As stated initially, we are subsequently focusing more on studies employing devices and materials that are more up-to-date. The constant and rapid evolution of all technologies related to CSII has many advantages. Nevertheless, a clear disadvantage is that even studies from 2008 might be outdated, as the given insulin pump/IIS is no longer being used. A given issue with an IIS might be resolved with a slight modification of a certain manufacturing process or a change in the design or materials/compounds used for the IIS. Such constant change—which can happen in intervals of some months and is often not widely announced—makes it difficult to draw more general conclusions that are relevant not only for now but for the future as well.

With respect to actual publications, in the nationwide pediatric surveillance of IISs in Germany and Austria, 192 (29%) patients reported that they had no IIS issues at all.[27] However, the other 475 (71%) patients reported 1404 events. With 33.9%, the most often observed event was IIS obstruction. A total of 14.2% of the patients reported that they had blood in the IIS; 11.1% had skin with redness, and 10.1% had bent cannula. It is impressive to see that 36.2% of the reported complications occurred by day 1 of IIS usage and 82.4% by the end of day 2.

An evaluation of the dermatological complications of IIS usage in 50 children and adolescents who were on CSII therapy for more than 6 months showed that 94% had scars with a diameter <3 mm, 66% had erythema not associated with nodules, 62% had SC nodules, and 42% had LHT.[51] An increased severity of skin problems was associated with lower adiposity (BMI); however, no correlation of the severity of dermatological problems was observed with metabolic control (hemoglobin A1c), site of IIS insertion, or insulin brand. Interestingly, an insertion of the needle of the IIS into the skin with an angle of 90° was associated with fewer problems than insertion at lower angles. Less than 5% of the patients considered stopping CSII because of dermatological problems. Another evaluation of dermatological side

effects and complications of CSII in school-age children and preschool-age children showed that skin problems are no more frequent or severe in very young children (<6 years) compared to school-age patients: scars <3 mm: 50% vs 75%; erythema: 25% vs 26%; nodules: 30% vs 21%; LHT: 45% vs 47%.[52] Blisters and local abscesses were rare in this study, and no participant required surgery. The calculated frequency of skin side effects per IIS usage year was 0.06 vs 0.04. None of the observed dermatological side effects led to discontinuation of CSII.

It appears that in the early years of CSII therapy, complications with infections at the infusion site were common and a frequent reason for termination of CSII.[41,43] Other studies suggest that infusion site problems are still an important factor for pump discontinuation.[38–40]

Issues Related to Metabolic Control

Insertion of a needle/catheter into the SC tissue will clearly cause a local trauma. In contrast to inserting a needle for some seconds into the skin with injection therapy, SC infusion with an IIS may lead to trauma for several days. This more extended local irritation leads to increased levels of proinflammatory cytokines in the interstitial fluid in the SC tissue, as shown both acutely and after up to 8 days of insertion.[53–55] This trauma can affect local blood flow and metabolism, which in turn could affect the absorption of insulin from the SC tissue. However, in the studies that demonstrated this local irritation, microdialysis catheters with a larger diameter in comparison to IIS were used, and fluid was pumped to and from the catheter, whereas with IIS, fluid is only pumped to the catheter. Therefore, it is not clear if the reported data can be transferred to IIS or not.

Interestingly, most pharmacokinetic studies evaluating the changes in serum insulin levels after giving boli with an insulin pump are quite old.[56–58] Furthermore, in these studies, the measurements were performed shortly (<12 h) after IIS insertion. So, in a study by Liu and colleagues,[59] the importance of IIS wear time was evaluated in 15 subjects with type 1 diabetes (T1DM) immediately after the IIS insertion and 3 days later. The authors reported a markedly reduced time to maximal plasma concentration (tmax) of insulin (Velosulin Human) on day 3 compared to day 0 without change in the total plasma exposure to insulin [unchanged area under the curve (AUC) 0–240 min]. In another study,[60] investigation of insulin (Velosulin Human) pharmacokinetics and IIS wear time was performed in 9 subjects with T1DM for approximately 12 h (day 1), 3 days, and 5 days after IIS insertion. In contrast to Liu and colleagues, no changes in insulin absorption rate or total plasma exposure to insulin were found on days 3 and 5 compared to day 1. The authors commented that plasma insulin profiles obtained in their study were similar to the profiles obtained on day 3 in the study by Liu and colleagues and that Liu and colleagues' finding of faster insulin absorption on day 3 may have been a result of retarded absorption on day 1. They speculated that since Liu and colleagues administered the first bolus immediately after IIS insertion, no SC insulin depot had been established, resulting in a delayed insulin absorption. It should also be mentioned that in the early years of pump therapy, the tubing of the IIS was made of polyvinylchloride, a plastic known to interfere with insulin much more than polyethylene, the material now used for tubing manufacturing.

Previous studies were performed with human insulin. Other published studies used insulin analogs.[32,61] Swan and colleagues[61]investigated the effect of age of the infusion site on insulin pharmacodynamics in 17 adolescents with T1DM using the two rapid-acting insulin analogs insulin lispro and insulin aspart. Unlike the other studies cited earlier, subjects used their preferred IIS in the gluteal region. A hyperinsulinemic (0.2 U/kg bolus) euglycemic clamp procedure was applied to determine insulin pharmacodynamics approximately 12 h (day 1) and 84 h (day 4) after IIS insertion. A significant reduction in time to maximal glucose infusion rate (t_{maxGIR}) and time to discontinuation of exogenous glucose was found on day 4 compared to day 1. However, the total effect of insulin (expressed by the AUC) was identical on both days. There was no difference between insulin lispro and insulin aspart.[61] The results of such studies have to be interpreted with caution; if the study design was flawed (was there a difference in the insulin depot on board during the two experimental conditions?), there is a high risk of comparing apples with oranges.

In general, some studies showed that prolonged use of one infusion site (days 3 to 4 compared to day 1 of infusion site use) results in earlier peak action and shorter duration of action of a standard bolus dose.[32,59,61] These data are in contrast to reports of unchanged absorption rate for regular insulin[60] and for insulin aspart.[62]

From a therapeutic point of view, the reported changes in insulin absorption over time induced by prolonged usage of the IIS are of concern. Schmid and colleagues[36] investigated the incidence of IIS-related events in correlation with the duration of IIS use under clinical conditions. This study shows that the patients could safely use the

IIS for at least 2 days; various skin and infusion set-related problems started to occur on the third day, partly requiring a change of the IIS. Even when patients locally tolerated a longer use of the IIS at the infusion site for up to 7 days, there appeared to be a steady increase in mean daily blood glucose concentrations. Another recent small pilot study also suggested a deterioration of metabolic control over time. Twenty patients used their IIS for up to 100 h; continuous glucose monitor recordings suggested a worsening of metabolic control from day 2 to day 5.[63] The authors concluded that the IIS should be changed every 48 h. However, both studies were suboptimal to investigate effects of IIS wear time on metabolic control. Adequately designed studies investigating optimal infusion set use time are still lacking.

As stated above, many clinicians find that some users can use an IIS longer than 4 or 5 days with keeping good metabolic control and no adverse events. It is not clear why there are such differences between patients.

Issues Related to Technical Aspects

It is not only the prolonged use of IIS that may cause problems with metabolic control in some patients. Design issues, manufacturing changes, and inappropriate instructions for use or training can also have an impact on IIS-related issues.

In general, part of the technical issues with IIS is related to the type of needle used. In particular, perpendicularly inserted soft cannulas entail the risk of kinking, bending, or crimping. This may go unnoticed either during the insertion process or during use. To minimize the risk of an incorrect insertion, the use of an insertion device is recommended for Teflon infusion sets. Clinicians report a significant number of failure rates (up to 10%) with autoinserters. This indicates room for improvement with the IIS design.

If the attachment of the IIS on the skin shifts laterally (e.g., in case of profound sweating), this can result in an IIS occlusion. It is also important that the connection of the IIS with the cartridge is not leaking; in the past, small leaks have led to several cases of diabetic ketoacidosis. Another issue is that in practice, the tubing easily gets caught if not attached to the body appropriately. The tubing is surprisingly sturdy (it is not easy to tear it in half), however, the needle and/or pump itself might be dislocated. Thus, not only the tubing can induce issues, it is the complete system (including the cartridge and the needle) that requires attention.

During use, the risk of soft cannula kinking and crimping can be reduced by ensuring proper application of the adhesive—sometimes even by additional taping. Users may also complain about leakage at the infusion set head, which is related to the movement of the cannula in the insertion channel and an insulin backflow.[64,65] With a better IIS design, such issues could be reduced. According to one insulin pump manufacturer's global complaint database (Roche Diabetes Care AG, data on file), the most common complaint with respect to metal needles is occlusion, but this also happens with Teflon catheters on a frequent basis. Often the reason for this cannot be exactly defined during the investigation at the manufacturer's site. Some data suggest that occlusion may be related to pricking of SC tissue, precipitation of insulin,[66] fibrin formation at the needle tip, and kinking of the soft cannula.[64] It appears as if a longer indwelling time (usage of one and the same IIS) is correlated with these events.[64]

Type and frequency of problems with the IIS may vary significantly. An observational, two-period study investigating 90° soft cannula infusion sets suggested that there are differences in the frequency of infusion set changes needed.[67] Liebner,[27] on the other hand, found no difference between steel and Teflon IISs. Unfortunately, no randomized head-to-head comparison of different IISs has been performed until now.

Recommendations for the Use of Insulin Infusion Sets and Patient Training

As IISs are not all equal, switching from one IIS to another one requires retraining, both by the patient and the diabetes team. It would be of interest to evaluate if there are differences between countries or teaching programs with respect to their focus on this topic. In addition, it is not clear if all patients are adequately trained at initiation of insulin pump therapy. Switching may be associated with reduced costs for the IIS, but the costs for training and potentially associated issues with a different IIS should be compared to the problem at hand before the switch. During the initial training session for a patient (and his/her family) in CSII therapy and also in the refresher sessions, appropriate handling of IISs by the patients themselves should be demonstrable. For example, patients should be instructed to disinfect the IIS insertion site appropriately, to switch the insertion area regularly to avoid skin related issues, and how to use the inserter adequately to reduce the failure rates of placing the IIS. Furthermore, there should be repeated training in the insertion and fixation process. It may

also be advantageous to select a steel IIS for patients initially starting insulin pump treatment, as the risk of insulin under-delivery due to a kinked or loose infusion set is reduced. With the switch to another infusion set, training has to be considered to avoid IIS issues. Again, depending on the simplicity of the IIS design, the time required for this training will vary.

According to manufacturer recommendations, IISs should be changed every 2–3 days. Regular replacement of the IIS is considered to avoid skin reactions and technical problems with pump and tubing, and it ensures a stable and reliable efficacy of the infused insulin. This is in contrast to a tendency in the reimbursement systems of some countries to direct patients into a more prolonged use of an IIS to reduce the costs associated with IISs. The potential medical consequences for the patient have to be balanced against economic considerations. It would be of financial benefit to the payer to have improved reliability and length of IIS wear. In such a discussion, one has to keep in mind the costs of supplies in pump therapy vs cost of the pump *per se*.

Questions for Development and Research: Conclusions and Discussion

During insulin pump therapy, there are a variety of ways that IIS issues can arise. These can be related to patient specificities as well as handling errors, but also to IIS-inherent problems. In order to reduce such issues, patients should be involved in the development process at an early stage. A more thorough evaluation after the launch of a new IIS also appears advisable. It appears as if there is no current postapproval monitoring available in the United States and Europe. The question is, do companies or regulatory authorities have data at hand from customer complaints that would allow evaluation of an association between a given IIS and the issues discussed in this review?

As many of the studies performed before the year 2000 were performed with outdated devices, had small sample sizes, and were not Good Clinical Practice studies, their relevance has to be viewed in the context of current standards, and repetition of such studies with up-to-date material is advisable.

After the fast-paced development of insulin pumps since the 1980s, there is also a need for improvement with IISs. This is confirmed by the fact that several mild IIS side effects are observed every day in clinical practice. Are these related to the IIS *per se,* and/or are these side effects more related to inappropriate patient training on IIS usage and poor patient compliance?

Fortunately, the number of complications arising from inflammation or infection appears to have decreased in recent years. Also, a considerable interindividual variability in successful length of wear has to be acknowledged. It is not clear what the predisposing factors are that lead a given patient to have skin and tissue reactions on onset of hyperglycemia. Studies with microdialysis catheters have shown increased levels of proinflammatory cytokines (33%) in the interstitial fluid acutely and after, for up to 8 days.[32] This suggests that there is an increase of inflammation enzymes in SC fatty tissue in some patients. Studies from the same research group from Denmark also showed that the adipose tissue blood flow (ATBF) is not constant during the wear-time of an IIS; it increased over time, i.e., from day 0 to day 2. But after 4 days, it was back to the level of day 0 in healthy subjects. In this study, the time to insulin peak decreased with IIS wear time.[32] However, in view of some shortcomings of the aforementioned studies, the questions are:

- What exact influence does ATBF have on insulin absorption, and how can we optimize it?
- Do we need more information on the recommended insertion depth for the IIS and the angle of insertion?
- Do we need more information about the cannula surface and shape to reduce damage and inflammatory reaction?
- Can a design change of the IIS tip reduce the frequency of problems, e.g., occlusions or glucose variations?
- Do we need more clinical studies, histological background information, or new cannula materials?
- Is usage of patch pumps associated with another set of complications? How do the respective frequencies change?
- How do sports, the menstrual cycle, exercise, fever, or other factors influence the selection of the cannula type or the frequency of IIS change?
- What is the impact of air in the infusion line on glucose fluctuations, and what is the reason for

air bubbles (an air bubble 10 cm long is equal to 1 U insulin)?

- Can focusing on the affixing of the IIS/adhesive during wear time reduce the number of IIS-related complications or glucose fluctuations?
- How important are human factors (e.g., ease of IIS insertion, convenience of usage) for patient acceptance of IIS and pump therapy in general?
- Can insulin delivery and glucose measurement be combined in one needle, and how is the reliability of both processes impacted over time?
- Is it imperative that infusion set manufacturers perform clinical trials before or after launching new infusion sets or modifying existing ones significantly?

One has to be careful in postulating a causal relationship between an observation and the IIS, i.e., its characteristics and application. In our opinion, those questions can be answered only by means of adequate clinical trials—ideally performed as head-to-head comparisons performed by independent researchers. Data generated in good surveillances can be used for hypothesis generation.

We are convinced that the focus has to lie on the development of safer IISs accompanied by a thorough scientific evaluation of the underlying physiological background. This will help to significantly reduce the frequency of IIS problems and to increase the acceptance of insulin pump therapy. It is also our hope that IISs will soon gain more attention as as a critical part of insulin pump therapy.

Funding:

This study was funded by Roche Diabetes Care AG, Roche, Burgdorf, Switzerland.

Acknowledgments:

We would like to thank Dr. Andreas Buhr of Roche Diabetes Care AG very much for his support with the literature search and the revision of the manuscript. We also explicitly thank Ruth Roberts, John Walsh, Andreas Thomas, and Bruce Buckingham, who contributed by sharing their clinical experience with respect to infusion set management during CSII.

Disclosures:

Lutz Heinemann is a consultant for a number of companies developing novel diagnostic and therapeutic options (including Roche Diagnostics). He is a partner of Profil Institut für Stoffwechselforschung, Neuss, Germany, and Profil Institute for Clinical Research, San Diego, CA. Lars Krinelke is an employee of Roche Diabetes Care AG, Roche, Burgdorf, Switzerland. He is Head of the Global Medical Affairs department for Insulin Delivery Systems.

References:

1. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care. 2003;26(4):1079–87.
2. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care. 2008;31 Suppl 2:S140–5.
3. Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, Waugh N. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess. 2010;14(11):iii–iv, xi–xvi, 1–181.
4. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, Siebenhofer A. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008;51(6):941–51. Epub 2008 Mar 20.
5. 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(7):765–74.
6. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F; European Society for Paediatric Endocrinology; Lawson Wilkins Pediatric Endocrine Society; International Society for Pediatric and Adolescent Diabetes; American Diabetes Association; European Association for the Study of Diabetes. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2007;30(6):1653–62.Epub 2007 Mar 19.
7. Heinemann L. Insulin pump therapy: what is the evidence for using different types of boluses for coverage of prandial insulin requirements? J Diabetes Sci Technol. 2009;3(6):1490–500.
8. Zisser HC. The OmniPod Insulin Management System: the latest innovation in insulin pump therapy. Diabetes Ther. 2010;1(1):10–24. Epub 2010 Sep 13.
9. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin. 2010;26(6):1519–30.
10. Frid A, Hirsch L, Gaspar R, Hicks D, Kreugel G, Liersch J, Letondeur C, Sauvanet JP, Tubiana-Rufi N, Strauss K; Scientific Advisory Board for the Third Injection Technique Workshop. New injection recommendations for patients with diabetes. Diabetes Metab. 2010;36 Suppl 2:S3–18.
11. Frid A, Hirsch L, Gaspar R, Hicks D, Kreugel G, Liersch J, Letondeur C, Sauvanet JP, Tubiana-Rufi N, Strauss K. The Third Injection Technique Workshop in Athens (TITAN). Diabetes Metab. 2010;36 Suppl 2:S19–29.
12. Scheiner G, Sobel RJ, Smith DE, Pick AJ, Kruger D, King J, Green K. Insulin pump therapy: guidelines for successful outcomes. Diabetes Educ. 2009;35 Suppl 2:29S–41S.

13. Heinemann L, Steiner S. Subcutaneous injection versus subcutaneous infusion of insulin: are the rates of absorption truly the same? J Diabetes Sci Technol. 2011;5(5):1027–9.

14. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. Diabetes Care. 1982;5(2):77–91.

15. Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL. Factors influencing the absorption, serum insulin concentration, and blood glucose responses after injections of regular insulin and various insulin mixtures. Diabetes Care. 1981;4(3):366–76.

16. Koivisto VA, Felig P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. Ann Intern Med. 1980;92(1):59–61.

17. Zehrer C, Hansen R, Bantle J. Reducing blood glucose variability by use of abdominal insulin injection sites. Diabetes Educ. 1990;16(6):474–7.

18. Bantle JP, Neal L, Frankamp LM. Effects of the anatomical region used for insulin injections on glycemia in type I diabetes subjects. Diabetes Care. 1993;16(12):1592–7.

19. Mudaliar SR, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care. 1999;22(9):1501–6.

20. Vora JP, Burch A, Peters JR, Owens DR. Absorption of radiolabelled soluble insulin in type 1 (insulin-dependent) diabetes: influence of subcutaneous blood flow and anthropometry. Diabet Med. 1993;10(8):736–43.

21. Frid A, Linde B. Intraregional differences in the absorption of unmodified insulin from the abdominal wall. Diabet Med. 1992;9(3):236–9.

22. Frid A, Linde B. Clinically important differences in insulin absorption from abdomen in IDDM. Diabetes Res Clin Pract. 1993;21(2–3):137–41.

23. Ter Braak EW, Woodworth JR, Bianchi R, Cerimele B, Erkelens DW, Thijssen JH, Kurtz D. Injection site effects on the pharmacokinetics and glucodynamics of insulin lispro and regular insulin. Diabetes Care. 1996;19(12):1437–40.

24. Bargero G, Capra Marzani M, Fasano M, Guazzo G, Minoglio A, Rosso A. [Relations between the site of insulin absorption and hypoglycemia in insulin-dependent diabetes during physical exertion]. Minerva Med. 1986;77(27):1285–8.

25. Koivisto VA, Felig P. Effects of leg exercise on insulin absorption in diabetic patients. N Engl J Med. 1978;298(2):79–83.

26. Van Faassen I, Razenberg PP, Simoons-Smit AM, van der Veen EA. Carriage of Staphylococcus aureus and inflamed infusion sites with insulin-pump therapy. Diabetes Care. 1989;12(2):153–5.

27. Liebner T, Holl R, Heidtmann B, Lilienthal B, Molz K, Hungele A, Bergheim I, Gialeli G. Insulinpumpenkatheter: Komplikationen im Kindes- und Jugendalter. Diabetologie und Stoffwechsel. 2011;6:S52.

28. 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(3):143–6.

29. Nguyen TV, Burnett JW. Local skin reaction caused by the plastic catheter tubing of the continuous subcutaneous insulin infusion system. Cutis. 1988;41(5):355–6.

30. Levandoski LA, White NH, Santiago JV. Localized skin reactions to insulin: insulin lipodystrophies and skin reactions to pumped subcutaneous insulin therapy. Diabetes Care. 1982;5 Suppl 1:6–10.

31. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol. 2003;4(10):661–7.

32. Clausen TS, Kaastrup P, Stallknecht B. Effect of insulin catheter wear-time on subcutaneous adipose tissue blood flow and insulin absorption in humans. Diabetes Technol Ther. 11(9):575–80.

33. Højbjerre L, Skov-Jensen C, Kaastrup P, Pedersen PE, Stallknecht B. Effect of steel and teflon infusion catheters on subcutaneous adipose tissue blood flow and infusion counter pressure in humans. Diabetes Technol Ther. 2009;11(5):301–6.

34. Kerr D, Morton J, Whately-Smith C, Everett J, Begley JP. Laboratory-based non-clinical comparison of occlusion rates using three rapid-acting insulin analogs in continuous subcutaneous insulin infusion catheters using low flow rates. J Diabetes Sci Technol. 2008;2(3):450–5.

35. Poulsen C, Langkjaer L, Worsøe C. Precipitation of insulin products used for continuous subcutaneous insulin infusion. Diabetes Technol Ther. 2005;7(1):142–50.

36. Schmid V, Hohberg C, Borchert M, Forst T, Pfützner A. Pilot study for assessment of optimal frequency for changing catheters in insulin pump therapy-trouble starts on day 3. J Diabetes Sci Technol. 2010;4(4):976–82.

37. Johansson UB, Adamson U, Lins PE, Wredling R. Patient management of long-term continuous subcutaneous insulin infusion. J Adv Nurs. 2005;51(2):112–8.

38. Schifferdecker E, Schmidt K, Boehm BO, Schatz H. Long-term compliance of intensified insulin therapy. Diabetes Res Clin Pract. 1994;23(1):17–23.

39. Wood JR, Moreland EC, Volkening LK, Svoren BM, Butler DA, Laffel LM. Durability of insulin pump use in pediatric patients with type 1 diabetes. Diabetes Care. 2006;29(11):2355–60.

40. De Vries L, Grushka Y, Lebenthal Y, Shalitin S, Phillip M. Factors associated with increased risk of insulin pump discontinuation in pediatric patients with type 1 diabetes. Pediatr Diabetes. 2011;12(5):506–12. Epub 2010 Aug 15.

41. Mecklenburg RS, Benson EA, Benson JW Jr, Fredlund PN, Guinn T, Metz RJ, Nielsen RL, Sanner CA. Acute complications associated with insulin infusion pump therapy. Report of experience with 161 patients. JAMA. 1984;252(23):3265–9.

42. Van Faassen I, Razenberg PP, Simoons-Smit AM, van der Veen EA. Carriage of Staphylococcus aureus and inflamed infusion sites with insulin-pump therapy. Diabetes Care. 1989;12(2):153–5.

43. Guinn TS, Bailey GJ, Mecklenburg RS. Factors related to discontinuation of continuous subcutaneous insulin-infusion therapy. Diabetes Care. 1988;11(1):46–51.

44. Chantelau E, Spraul M, Mühlhauser I, Gause R, Berger M. Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for type 1 (insulin-dependent) diabetes mellitus: a one centre experience. Diabetologia. 1989;32(7):421–6.

45. Bruttomesso D, Pianta A, Crazzolara D, Scaldaferri E, Lora L, Guarneri G, Mongillo A, Gennaro R, Miola M, Moretti M, Confortin L, Beltramello GP, Pais M, Baritussio A, Casiglia E, Tiengo A. Continuous subcutaneous insulin infusion (CSII) in the Veneto region: efficacy, acceptability and quality of life. Diabet Med. 2002;19(8):628–34.

46. Teutsch SM, Herman WH, Dwyer DM, Lane JM. Mortality among diabetic patients using continuous subcutaneous insulin-infusion pumps. N Engl J Med. 1984;310(6):361–8.

47. Centers for Disease Control (CDC). Toxic-shock syndrome in a patient using a continuous subcutaneous insulin infusion pump-Idaho. MMWR Morb Mortal Wkly Rep 1983;32(31):404–6, 412.

48. Nowakowska M, Jarosz-Chobot P, Polańska J, Machnica Ł. Bacterial strains colonizing subcutaneous catheters of personal insulin pumps. Pol J Microbiol. 2007;56(4):239–43.

49. Chantelau E, Lange G, Sonnenberg GE, Berger M. Acute cutaneous complications and catheter needle colonization during insulin-pump treatment. Diabetes Care. 1987;10(4):478–82.

50. Chantelau E, Lange G, Gasthaus M, Boxberger M, Berger M. Interaction between plastic catheter tubings and regular insulin preparations used for continuous subcutaneous insulin-infusion therapy. Diabetes Care. 1987;10(3):348–51.

51. Conwell LS, Pope E, Artiles AM, Mohanta A, Daneman A, Daneman D. Dermatological complications of continuous subcutaneous insulin infusion in children and adolescents. J Pediatr. 2008;152(5):622–8. Epub 2008 Jan 22.

52. Schober E, Rami B. Dermatological side effects and complications of continuous subcutaneous insulin infusion in preschool-age and school-age children. Pediatr Diabetes. 2009;10(3):198–201. Epub 2008 Nov 3.

53. Murdolo G, Herder C, Wang Z, Rose B, Schmelz M, Jansson PA. *In situ* profiling of adipokines in subcutaneous microdialysates from lean and obese individuals. Am J Physiol Endocrinol Metab. 2008;295(5):E1095–105. Epub 2008 Sep 9.

54. Pachler C, Ikeoka D, Plank J, Weinhandl H, Suppan M, Mader JK, Bodenlenz M, Regittnig W, Mangge H, Pieber TR, Ellmerer M. Subcutaneous adipose tissue exerts proinflammatory cytokines after minimal trauma in humans. Am J Physiol Endocrinol Metab. 2007;293(3):E690–6. Epub 2007 Jun 19.

55. Wisniewski N, Rajamand N, Adamsson U, Lins PE, Reichert WM, Klitzman B, Ungerstedt U. Analyte flux through chronically implanted subcutaneous polyamide membranes differs in humans and rats. Am J Physiol Endocrinol Metab. 2002;282(6):E1316–23.

56. Lauritzen T, Pramming S, Deckert T, Binder C. Pharmacokinetics of continuous subcutaneous insulin infusion. Diabetologia. 1983;24(5):326–9.

57. Hirsch IB, Farkas-Hirsch R, McGill JB. Catheter obstruction with continuous subcutaneous insulin infusion. Effect of insulin concentration. Diabetes Care. 1992;15(4):593–4.

58. Wiefels K, Hübinger A, Dannehl K, Gries FA. Insulinkinetic and -dynamic in diabetic patients under insulin pump therapy after injections of human insulin or the insulin analogue (B28Asp). Horm Metab Res. 1995;27(9):421–4.

59. Liu D, Moberg E, Wredling R, Lins PE, Adamson U. Insulin absorption is faster when keeping the infusion site in use for three days during continuous subcutaneous insulin infusion. Diabetes Res Clin Pract. 1991;12(1):19–24.

60. Olsson PO, Arnqvist H, Asplund J. No pharmacokinetic effect of retaining the infusion site up to four days during continuous subcutaneous insulin infusion therapy. Diabet Med. 1993;10(5):477–80.

61. Swan KL, Dziura JD, Steil GM, Voskanyan GR, Sikes KA, Steffen AT, Martin ML, Tamborlane WV, Weinzimer SA. Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. Diabetes Care. 2009;32(2):240–4. Epub 2008 Nov 18.

62. Bode BW, Strange P. Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. Diabetes Care. 2001;24(1):69–72.

63. Thethi TK, Rao A, Kawji H, Mallik T, Yau CL, Christians U, Fonseca V. Consequences of delayed pump infusion line change in patients with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion. J Diabetes Complications. 2010;24(2):73–8. Epub 2009 Apr 23.

64. Mecklenburg RS, Guinn TS, Sannar CA, Blumenstein BA. Malfunction of continuous subcutaneous insulin infusion systems: a one-year prospective study of 127 patients. Diabetes Care. 1986;9(4):351–5.

65. Pickup JC, Sherwin RS, Tamborlane WV, Rizza RA, Service FJ. Conference on insulin pump therapy in diabetes. Multicenter study of effect on microvascular disease. The pump life. Patient responses and clinical and technological problems. Diabetes. 1985;34 Suppl 3:37–41.

66. Peden NR, Braaten JT, McKendry JB. Diabetic ketoacidosis during long-term treatment with continuous subcutaneous insulin infusion. Diabetes Care. 1984;7(1):1–5.

67. Renard E, Guerci B, Leguerrier AM, Boizel R; Accu-Chek FlexLink Study Group. Lower rate of initial failures and reduced occurrence of adverse events with a new catheter model for continuous subcutaneous insulin infusion: prospective, two-period, observational, multicenter study. Diabetes Technol Ther. 2010;12(10):769–73.