The Injection Technique Factor: What You Don't Know or Teach Can Make a Difference

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IN BRIEF To be consistently effective, insulin must be delivered into subcutaneous tissue. If insulin is delivered intramuscularly, its uptake and action become variably faster, leading to suboptimal, inconsistent glucose control. The best strategy to avoid intramuscular injection is to use the shortest needles available. Injection sites should be rotated systematically to prevent lipohypertrophy, which also substantially affects insulin uptake and action. New evidence-based insulin delivery recommendations are available, and awareness of them should lead to more effective use of insulin therapy, improved clinical outcomes, and considerable cost savings.

Glucose variability with episodes of hyper- and hypoglycemia is a challenge for all insulin-using patients, especially those with type 1 diabetes. Clinicians tend to focus on the type and amount of insulin given versus the nutrition intake when reviewing patient glucose logs or meter downloads. Nevertheless, how insulin is given (i.e., the insulin injection technique [IT]) may be as important as the insulin dose.

The desired tissue for insulin delivery is the subcutaneous (SC) fat because insulin absorption (pharmacokinetics [PK]) and action (pharmacodynamics [PD]) in the SC space are much more consistent than when it is delivered as an intramuscular (IM) injection. However, many needles for insulin pens and syringes are now known to be too long, raising the risk of IM injections. IM injection can markedly (and variably) increase insulin uptake, depending on whether the muscle is at rest or exercised (1). To mitigate this risk, patients are often taught to lift skinfolds or to angle the needle 45° from the skin. A more practical approach is to simply switch patients to shorter needles.

Another concern of improper IT is the development of lipohypertrophy (LH). LH has been shown to affect ≥50% of injecting patients (2–5). Improper injection site rotation and needle reuse are the most common factors associated with LH. Injecting into LH reduces insulin absorption and action, raises postprandial glucose, and greatly increases insulin uptake variability (6). Despite this, inspection of injection sites is not routinely performed by health care professionals (HCPs) or patients, hence, the "unexplained" nature of many blood glucose fluctuations.

Consensus recommendations for insulin delivery were recently published by clinicians participating in the FITTER (Forum for Injection Technique and Therapy: Expert Recommendations) workshop in October 2015 (7). FITTER was the most recent in a series of workshops on insulin delivery. FITTER recommendations are largely based on the results of the most recent Injection Technique Questionnaire (ITQ) survey conducted in 2014–2015. In

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that survey, 13,289 insulin-injecting patients from 42 countries were queried in detail about their personal injection practices and were examined by a diabetes nurse or doctor (8,9). Results are available online (10).

This review explains why proper IT makes insulin action more reliable and predictable.

Insulin Usage and Action

Approximately half a billion people in the world have diabetes (11). All people with type 1 diabetes and ~ 20–25% of those with type 2 diabetes use insulin, usually via injections. There are an estimated 150–200 million insulin users in the world (12). Insulin is the most effective glucose-lowering medication for diabetes, but it also has one of the lowest therapeutic indexes of any medication and is regularly listed as high risk or high alert by the Institute for Safe Medication Practices (13). This risk can be increased by improper IT.

Insulin kinetics are derived from carefully controlled PK studies of healthy subjects at rest. In the clinical world, however, many factors affect PK (insulin uptake), including whether insulin is delivered into SC fat or as an IM injection. Needles that are too long pose a substantial risk of IM injection, which leads to erratic uptake—only slightly faster than SC injection at rest but variably and substantially increased with light or more intense exercise (1). Such PK disturbances lead to glycemic variability and increase the risk of hypoglycemia.

Skin and SC Thickness

SC insulin deposition requires that the delivery device completely crosses the skin (epidermis and dermis) into the fat, but not go so deep as to reach the fascia or muscle. Mean skin thickness is ~2.0–2.5 mm, with a 95% CI of 1.3–3.3 mm. Skin thickness is remarkably similar across injection sites, sexes, ethnicities, age-groups, and BMI categories. This has been shown in studies from China, India, the Philippines, and Korea (all mainly in people with type 2 diabetes) (14–17); from the United States (in adults with either type 1 or type 2 diabetes, including those from four distinct ethnic groups) (18); and from South Africa and Italy (in children with type 1 diabetes) (19,20). Skin is slightly thinner at the limbs versus at truncal sites and in children versus adults, but these distinctions are clinically irrelevant because they involve only fractions of a millimeter.

However, SC adipose tissue thickness is highly variable depending on BMI, sex, and site of injection. Postpubertal females have, on average, 5 mm more SC fat than men, site for site, when controlling for BMI. In both sexes, truncal sites (abdomen and buttocks) contain more fat than do limbs (arm and thigh). The higher the BMI, the thicker the SC fat (18,21).

Infants until the age of 2 years have more SC tissue than do preschool children. Children from 2 to 6 years of age have little SC tissue regardless of sex. From 7 to 13 years of age, children gain SC tissue progressively, but SC tissue thickness is almost identical in both sexes until puberty (22). At puberty, SC thickness increases more rapidly in females than in males, reflecting the influence of estrogen.

The distance from skin surface to muscle fascia largely depends on SC tissue thickness; thus, comparing this total distance to the available needle lengths determines the risk of IM injection site by site (20–22). The key message is that shorter needles lower the risk of IM injection.

Current Practices in Need of Revision: Switch to Short

It is now widely recognized that 4-mm pen needles are appropriate for all injecting patients, whether they are adults or children, thin or obese, female or male, or from any ethnicity (23). These short needles are key to reducing IM injection risk while maintaining equivalent glycemic control. As recently as 2010, 8-mm needles were used worldwide by ~50% of all injecting patients (24), but since then, their use has declined precipitously, while the use of shorter needles has increased rapidly.

The most recent ITQ survey (2014–2015) showed that ~30% of patients use needles ≥8 mm, that 5- and 6-mm needles are used by 20% each, and that 30% of patients worldwide use 4-mm needles (8); in other words, "short" pen needles (4- and 5-mm) are now used by half of all patients worldwide, and the use of 4-mm needles equals that of 8-mm needles. However, there are still concerns: needles ≥4 mm in length are being used by many patients in sites where the risk of IM injection is very high (arms and thighs) and by patients who have an increased risk because of lower SC fat thickness (normal-weight and slim adults, as well as all children and adolescents).

Appropriate Needle Lengths, IT, and Clinical Outcomes

Multiple studies have shown that needle length has virtually no effect on glycemic control, including in obese patients (25–32). However, needle length is crucial for correct insulin deposition (SC vs. IM). The shortest pen needle is 4 mm in length, and the shortest syringe needle is 6 mm. The longer the needle is, the greater the risk of IM injections will be. Furthermore, most HCPs are not aware that longer needles usually have a larger diameter, which makes them more painful (33) and possibly contributes to more frequently skipped injections.

A series of controlled clinical trials, nearly all crossover in design, have consistently demonstrated equivalent glycemic control, less pain, greater patient preference, and no increase in skin backflow or leakage for the 4-mm pen needle versus longer needles (23,34–37). These results included obese American patients with BMIs of up to nearly 60 kg/m^2, some of whom were taking high doses of glargine (>40 units/injection) and had a total daily dose (TDD) of insu-

lin of up to 300 units/day (38). These findings are explained by the fact that insulin absorption is the same regardless of how deep it is injected into fat, as long as it remains in the SC fat (36,39,40).

In summary, the 4-mm needle inserted perpendicularly is long enough to penetrate the skin and enter SC fat, with little risk of IM injection. It should be considered the safest pen needle for adults and children regardless of age, sex, ethnicity, or BMI. This needle should be inserted perpendicular to the skin (90° to skin surface), never at an angle, regardless of whether a skinfold is raised. Very young children (≤6 years of age) and very thin adults (BMI <19 kg/m^2) should lift a skinfold ("pinch up") and insert the 4-mm needle perpendicularly into it. Others may use the 4-mm needle without lifting a skinfold. Patients with tremors or other disorders that make them unable to hold a 4-mm pen needle in place may need longer needles.

If 4-mm needles are not available, 5-mm needles may be used with a lifted skinfold. Similarly, 6-mm needles are another option provided patients use a skinfold and inject at a 45° angle. (Injections at this angle effectively deposit insulin at a 4-mm depth.) Use of 6-mm needles should be strongly discouraged in children ≤6 years of age. In one study of 6-mm needles in children and adolescents with type 1 diabetes, pinching up in the abdomen nearly doubled the SC fat thickness (as desired), but in the same subjects, doing a pinch-up in the thigh only increased the thickness 22%, and in thinner subjects, it actually decreased the SC fat, increasing the risk of IM injection (41). Skin leakage may also be increased by this procedure (42).

Recommended injection sites include the abdomen, lateral thigh, arms, and buttocks (43–47). Insulin analogs (both fast-acting and basal) may be injected at any site with similar absorption/action profiles (48). Conventional (human) insulins such as regular and NPH show site-specific absorption characteristics (1,49,50). These insulins are absorbed fastest from the abdomen and arm and slowest from the thigh and buttocks.

Local Complications

LH is the most frequent local complication of both insulin injections (2–5) and infusions (51,52), with prevalence rates ≥50% in multiple studies in various countries. HCPs taking care of insulin-injecting patients should make it a habit to check for LH frequently (at least yearly), especially if there are patterns of high glucose variability and unexplained hypo- and hyperglycemia.

For the moment, there is no gold standard for diagnosis of LH other than visual observation and palpation. LH lesions usually display a texture change in the fat that has been variably described as "rubbery," "nodular," "edematous," or "hardened." Using a lubricating gel when examining for LH greatly improves the sensitivity for detecting this textural change. Gentile et al. (53,54) have shown convincingly that HCPs trained to detect LH can do so with high efficiency using the physical exam alone, achieving up to 97% consistency levels.

Factors associated with LH (but not yet causally proven) are time on insulin (the longer the duration of insulin therapy, the greater the risk will be), a higher number of daily injections, failure to space injections far enough apart (at least 1 cm), and extensive reuse of needles, defined by one well-done study (2) as injecting ≥5 times with a single needle (2,4,55–58). Only the last two risk factors are modifiable.

Insulin injected into LH results in delayed or erratic absorption (PK), which has adverse effects on insulin action (PD) and consequently may worsen glycemic control (59–62). A recent crossover glucose clamp study demonstrated that both insulin PK and PD are blunted with injection into LH areas, with 3–5 times more variability than injecting the same dose into normal areas. A controlled mixed-meal tolerance test in the same study showed prolonged hyperglycemia after premeal injection into LH tissue as well (6). The key message here is that insulin should never be injected into LH tissue.

Most studies of LH report that affected patients have a significantly higher insulin TDD than patients without LH (2,4,63,64). Higher insulin doses related to LH lead to substantial increases in direct costs for individual patients or payers. In one study, patients with LH used an average of 15 units/day more of insulin than those without LH (2). Subsequent studies have shown comparable results (4,63,64).

When patients shift from injecting insulin into LH and begin using normal tissue, they risk provoking hypoglycemia if they continue with the same doses. A decrease in insulin dose is required; this varies from patient to patient and should be guided by frequent self-monitoring of blood glucose (SMBG). Reductions of 20% from the original (intra-LH) dose are common (56,65). There should be no tapering down; the 20% reduction must begin with the first injection into normal tissue. After that, patients may have to titrate their doses based on SMBG results. The process must be individualized and is based somewhat on trial and error. Careful HCP guidance must be provided.

Injections should be rotated systematically by spacing them at least 1 cm (about the width of an adult finger) from each other; this helps to avoid repeat tissue trauma. One approach involves dividing sites into quadrants (or halves when using the buttocks or thighs), using one quadrant per week and moving from quadrant to quadrant in a consistent direction (e.g., clockwise). Patients should rotate injections between sites, as well as within a site. HCPs treating LH also recommend against excessive reuse of needles, which leads

to abnormal traumatizing of the skin and underlying structures.

Needle Reuse

Patients commonly reuse needles, mainly for reasons of convenience and cost-savings. However, a number of studies have linked needle reuse to LH (2,4,24,55,56,66), especially when reuse frequency is excessive (≥5 times/needle) (2). Injection pain was associated with reuse in one study, although this was not confirmed in another report (67,68). Bacterial growth was found on reused needles and inflammatory changes (skin redness) were found at injection sites of patients who reused needles (69,70). Although local infections or abscesses have not been documented with needle reuse, FITTER recommendations advise against reusing needles (7), which are labeled by regulatory agencies for single use. A meta-analysis of 25 studies could not give a conclusion regarding whether needle reuse was acceptable (71).

Sharps Safety

Patients should never share insulin pens, whether in the hospital or home setting. Blood can be aspirated back into the pen cartridge even after one injection, and this could possibly transmit a blood-borne disease such as HIV or hepatitis to subsequent users, even if they use a new pen needle. Sonoki et al. (72) found hemoglobin in a number of cartridges that patients had used only once. Le Floch et al. (73) reported similar results, and a recent U.S. study corroborated these findings (74). The rule with insulin injections is clear: one patient/insulin pen.

Safety-engineered devices play a crucial role in protecting injectors, pump users, and downstream workers from needle stick injuries (75). Furthermore, needle recapping in the health care setting should simply not be done because it brings HCPs' fingers into the immediate proximity of contaminated needle tips. Sharps containers must be easily accessible at the point of care, beside the patient, before the injection or infusion is performed. Safe disposal should be taught to patients, caregivers, and all others who may come into contact with the sharp device from the beginning to the end of the injection or infusion therapy and reinforced throughout (76). Under no circumstances should sharps material be disposed of into the public trash or rubbish system.

Role of HCPs

Optimal insulin delivery is more complex and involves choices that patients and HCPs may not have previously considered. These include the choice of injection sites as a function of the insulin delivered; the choice of needle length as a function of SC thickness; injection or infusion technique to ensure consistently effective SC delivery; precise and systematic rotation of delivery sites; injection site examination for LH; and reduced reuse of needles and safe disposal of used sharps to reduce needle-stick injury risk to family members or the community at large (7,77).

Even when device use seems easy, as with pens, lack of proper IT can lead to seemingly mindless and possibly dangerous errors (78). HCPs are often surprised to learn that insulin delivery is suboptimal in multiple ways: preparing for injection, drawing up insulin (syringe users), priming (pen users), preparing correct doses, and injecting insulin. Hence, it is of utmost importance to have patients demonstrate their IT to their HCP. Pen users in one study were particularly likely to omit or make mistakes at key steps (79). Well-documented cases have been reported in which incorrect insulin pen/pen needle usage such as not removing the inner pen needle shield resulted in full-blown ketoacidosis and fatality in patients with type 1 diabetes, due to failure to administer any insulin (80).

IT Training and Clinical Outcomes

A multicenter prospective interventional study in insulin-injecting patients showed that education focused on these recommendations (systematic rotation and single use of needles) led to significantly reduced detectable LH after only 6 months, with LH lesions either disappearing or decreasing by up to 50% from their original size. Mean A1C values decreased by >4 mmol/L (>0.5%), and there were significantly lower rates of unexplained hypoglycemia and glucose variability. The mean insulin TDD decreased by 5.6 units from a baseline of 71.6 units/day (63).

In a controlled, multicenter, prospective study in patients with LH (64), the intervention contained repeated instructions to shift injections to non-LH areas, to rotate correctly within injection sites, to avoid needle reuse, and to switch to 4-mm needles to facilitate rotation without increasing the risk of IM injections. Patients were also given intensive education on many of the issues summarized in this review. Control patients were told of the presence of LH and advised once that injections should not be made into LH. They received the standard education offered at that site.

The intervention group in this study showed a significant decrease in TDD of ~5 units from baseline (P = 0.035). Both intervention and control groups had significant decreases in A1C (up to 0.5%), but the between-group difference in A1C change was not significant. A significant percentage of intervention patients improved their IT habits. The authors concluded that the intervention was effective in both groups, but that intensive education led to faster and better outcomes.

In a randomized interventional pilot study, three groups of patients with either type 1 or type 2 diabetes were followed for 6 months (81). Two groups received structured IT training (with one receiving 4-mm needles for every injection, whereas the other did not) and a control group that got neither training nor needles. Both trained groups saw A1C reductions of

TABLE 1. Top 10 IT Recommendations

1. Have patients demonstrate their IT, either by performing an actual injection or by injecting into a pad or foam pillow. Use this as a teaching occasion, praising what they do correctly and correcting any improper practices.
2. Injections should only be given into clean, healthy sites using clean hands. Disinfecting the skin is generally not required.
3. Injections must be given subcutaneously, not intramuscularly. The 4-mm pen needle has the lowest risk of IM injection and allows wider zones for rotation.
4. Needles that are 12.7 mm in length are not recommended for any patients, and patients who are using 8-mm needles should be switched to shorter lengths.
5. The 4-mm needle is preferred for all injectors regardless of age, sex, ethnicity, or BMI. It should be inserted perpendicular to the skin (90° to skin surface)—not at an angle—regardless of whether a skinfold is raised.
6. Very young children (≤6 years of age) and very thin adults (BMI <19 kg/m^2) should always inject with the 4-mm needle into a lifted skinfold. Other children, adolescents, and adults may inject without a skinfold.
7. Inspect patient injection sites at least annually, both visually and by palpation using gel to aid in detection of LH. Make patients aware of the presence of any LH, and instruct them not to inject into it. Use the LH lesion to teach them what to feel and look for and engage them in surveying their injection sites.
8. If LH is found, switch injections to normal tissue while decreasing the dose of insulin. Reductions often exceed 20% of the original dose. Monitor SMBG results closely.
9. Rotate injections systematically to avoid LH, injecting at least 1 cm (approximate width of an adult finger) from previous injections.
10. If possible, patients should avoid reusing needles, which are sterile, one-use devices. Excessive reuse (more than five times) has been associated with LH.

~1%, but the nontrained group had no change in A1C. LH and needle reuse declined and IT improved in both of the trained groups, but these changes did not occur in the nontrained group.

Conclusion

All of the issues raised by this review can be addressed through targeted education by HCPs and proper training (Table 1). There should be no doubt that virtually all patients should use 4-mm pen needles (always at a 90° angle to the skin surface), 5-mm pens (with a pinch-up), or 6-mm needles (at a 45° angle with either pen or syringe). Needles ≥8 mm in length should be avoided. Patients should rotate sites correctly to avoid LH. HCPs should inspect injection sites regularly, observe patients' or caregivers' IT, and provide targeted, individualized instruction on LH prevention and on LH treatment if it is present.

If adopted, all of the interventions we propose will result in fewer unexpected hypoglycemic episodes and less glycemic variability. None of the recommendations requires major changes in the health care system. All can be attained by the creation of awareness, a reassessment of our training techniques, removal of barriers, and the provision of appropriate educational tools.

Duality of Interest

The authors are employees of BD, a manufacturer of injecting devices.

Author Contributions

L.J.H. reviewed and edited the manuscript. K.W.S. researched data, reviewed the literature, and wrote the manuscript. KW.S. is the guarantor of this work and, as such, had full access to all the supporting data and takes responsibility for the accuracy and integrity of the text.

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