Chapter 4

Optimal Insulin Delivery

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Additional information is available at the end of the chapter

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Abstract

Insulin therapy is only effective if it is delivered into the right tissue in the right way. Exogenous insulin is intended for the subcutaneous (SC) tissue, not the muscle or skin. If delivered into the latter, its absorption (pharmacokinetics (PK)) and action (pharmacodynamics (PD)) are unpredictable, which often leads to poor glucose control. Correct insulin therapy begins with matching the insulin to the site used. Typically, four sites are used for insulin injection or infusion: the abdomen lateral to the umbilicus all the way to the flanks, the anterior lateral upper half of the thigh, the deltoid region of the arm, and the upper outer quadrant of the buttocks. Regular insulin and neutral protamine Hagedorn (NPH) are both absorbed more rapidly from the arm and abdominal sites and more slowly from the thigh and buttocks. The newer insulin analogs, both rapid- and slow-acting, do not appear to be influenced by the site used for injection. In order to avoid intramuscular (IM) injections, patients should use the shortest needles currently available (the 4-mm pen needle and the 6-mm syringe needle). Very young children should raise a skin fold and inject into it even when using the 4-mm needle. Giving injections with the 6-mm needle at a 45° angle converts this needle into the equivalent of the 4 mm. Injection sites should be rigorously rotated, with the new injection being approximately 1 cm from previous injections. This measure helps prevent the most common complication of injection therapy, lipohypertrophy (LH). Injecting into LH leads to unstable PK and PD and deregulated glucose control, manifested as unexpected hypoglycemia, glycemic variability, and elevated HbA1c values. Comprehensive insulin deliver recommendations have recently been published.

Keywords: insulin, injection needles, subcutaneous, lipodystrophy, lipohypertrophy

1. Introduction

Current insulin therapy requires delivery into the subcutaneous (SC) tissue either by injection or by infusion. Optimal insulin delivery requires that accidental intramuscular (IM) or

intradermal (ID) delivery be avoided since the pharmacokinetics (PK) and pharmacodynamics (PD) of insulin are significantly altered in these tissue spaces. Optimal delivery also requires that sites of injection or infusion be rotated systematically in order to avoid the most common complication of insulin therapy, lipohypertrophy (LH). Insulin delivered into LH also has significantly altered PK and PD, which can lead to unexpected hypoglycemic episodes and glycemic variability. The latter are associated with worsened overall glucose control, increased short- and long-term complications, and higher costs.

Recently, new recommendations have been published as a consensus document from international diabetes experts [1]. This publication was the collective output of 183 experts from 54 countries who wrote and vetted a practical, evidence-based roadmap for optimal insulin delivery at the FITTER (Forum for Injection Technique and Therapy: Expert Recommendations) workshop from October 23 to 24, 2015, in Rome. FITTER was the fourth in a sequence of workshops on optimal insulin delivery [2–4]. The FITTER recommendations were also based on the results of the fourth Injection Technique Questionnaire (ITQ) survey conducted from 2014 to 2015. In total, 13,289 insulin-injecting patients from 42 countries participated [5].

Each recommendation is followed by a grade (e.g., A2). The letter indicates the strength of each recommendation: A. Strongly recommended; B. Recommended; C. Unresolved issue. The number indicates the degree of scientific support for each recommendation: 1. At least one rigorously performed study which is peer-reviewed and published; 2. At least one observational, epidemiologic, or population-based study which is peer-reviewed and published; 3. Consensus expert opinion based on patient experience. Since FITTER, many diabetes groups from countries around the world have adapted and adopted these recommendations as local guidelines. We draw on certain of these recommendations in the review that follows as well as summarize studies that have been performed since FITTER and will follow a thematic format, beginning with the anatomy of injection sites.

2. Current insulin delivery practice

A large survey of current insulin delivery has shown that there are many aspects of injection practice which are suboptimal [5, 6]. For decades, professionals had been advising patients to use insulin needles which, we now know, were too long for them, with no scientific rationale. However, after the shortest pen needles (4 mm) became available and studies on injection site anatomy and needle performance began to be published, starting in 2010 [7, 8], showing the safety and efficacy of these needles, the recommendations of experts changed. It was recognized that 4-mm pen needles were the optimal choice for nearly all injecting patients, whether adults or children: thin, normal-weight or obese, male or female, and of all ethnicities. These needles were felt to be a key step toward reducing the risk of IM injections. As a result, the use of the 8-mm needle, the dominant size in 2010, has decreased dramatically since then, with a corresponding increase in the use of the 4-mm needle.

However, the latest survey revealed that the longer lengths (8 mm and higher) are still being used by approximately 30% of patients worldwide and that the 5- and 6-mm needles are still used by approximately 20% each. This means that only 30% of patients worldwide currently use the recommended 4-mm needles. Longer needles are being used in sites where IM injection risk is very high (thighs and arms) and by patients who are at an increased risk because they have thin SC layers (slim and normal-weight adults as well as all adolescents and children).

The same survey has shown that lipohypertrophy (LH) is very common at injection sites. LH was found in almost a third of patients worldwide, many of them having LH at multiple injection sites. Injecting into LH has serious consequences for glucose control as well as possibly adverse effects on long-term outcomes and costs. Patients with LH consume a mean of over 10 IU more insulin per day than those without LH, and their HbA1c is on average 0.55% higher. LH is associated with increased rates of unexplained hypoglycemia, glucose variability, and more frequent diabetic ketoacidosis (DKA).

The survey showed that LH is most frequently associated with an incorrect rotation of injection sites and reusing pen needles. Rotating injection sites carefully appears to be the best method of avoiding LH. HbA1c values are lower in patients who rotate their injections over larger injection areas and who get their sites inspected regularly. Checking of injection sites routinely by health-care givers is associated with less LH and lower HbA1c levels, yet nearly 40% of patients reported that they could not remember their injection sites ever being examined. Patients are also more likely to rotate correctly if they have obtained injection instruction from their carer in the last 6 months. However, less than two out of five claim to have obtained such instructions on injecting in that time period. Ten percent of total injectors claim that they have never obtained injection training at all. The survey also shows that incorrect disposal of sharps after use is rampant. The majority of used sharps end up in public trash and constitute a major risk factor for accidental needle sticks.

3. Skin thickness

The skin is the main obstacle the needle must overcome. Needles must be at least long enough to traverse the skin and reach the SC tissue. Adult skin, according to a number of studies using imaging techniques ranging from ultrasound (US) to computer tomography (CT), has yielded remarkably similar results across genders, ethnicities, age groups, and body mass index (BMI) categories. The skin averages approximately 2–2.5-mm thick and varies in its 95% confidence interval (CI) between 1.25 and 3.25 mm. These studies included patients with type 2 diabetes (T2DM) from the Philippines [9], Korea [10], China [11], and India [12]; both type 1 diabetes (T1DM) and T2DM adults from the USA (including four different ethnic groups) [7]; and children from South Africa [13] and Italy [14].

The skin in children is slightly thinner than in adults, but these differences are largely irrelevant for insulin infusions and injections. Skin thickness increases during adolescence and reaches adult size in the late teens.

4. SC thickness

The SC tissue is the target for insulin. Injections must reach the SC tissue, but not go deeper into the muscle fascia or the muscle itself. Therefore, the thickness of the SC is critical in determining the desired length of the needle as well as the injection technique (e.g., lifting a skin fold or not). SC tissue thickness varies widely depending on gender, site of injection, and BMI. Women, on average, have approximately 5-mm thicker SC fat than men, when one controls for BMI and body site. Truncal sites (abdomen and buttocks) have more SC fat than limbs (arm and thigh), in the same patient. The higher the BMI, the thicker the SC fat. Studies within the last decade have used precision US to determine the SC tissue thickness in a diverse group of adults [7, 9, 15, 16], adolescents, and children [13, 14].

Needle length	Combined	Thigh	Arm	Abdomen	Buttock
4 mm	0.4%	1.6%	1.0%	0.3%	0.1%
5 mm	1.8%	4.7%	3.1%	1.1%	0.5%
6 mm	5.7%	10.0%	7.0%	2.8%	1.3%
8 mm	15.3%	25.0%	19.5%	9.7%	5.5%
12.7 mm	45.0%	63.0%	55.0%	38.0%	26.9%

*Assumes injection straight at 90° without pinch-up (the table adapted from Hirsch [16]).

With kind permission from Hirsch L et al. [16]. Intramuscular risk at insulin injection sites—measurement of the distance from the skin to the muscle and rationale for shorter-length needles for subcutaneous insulin therapy.

Table 1. Estimated IM injection risk in adults, by body site*.

	Marran, 2014 [13]				Lo Presti, 2014 (pooled) [14]		
	Arm	Thigh	Abdomen	Buttock	Ages 2–6	Ages 7–13	Ages 14–17
4 mm	27.5%	12.5%	12.5%	0%	20.2%	4.6%	2.4%
5 mm	47.5%	22.5%	30.0%	0%	46.0%	18.4%	16.1%
6 mm	62.5%	30.0%	37.5%	5.0%	66.5%	38.0%	34.5%
8 mm	87.5%	62.5%	50.0%	15.0%	83.9%	65.3%	66.1%
12.7 mm	100%	90.0%	85.0%	35.0%	97.2%	93.9%	96.4%

*Assumes that injections are into flat skin and not into lifted skin fold.

Table 2. Calculated risk of IM injection in children and adolescents as a function of injection site, age, and needle length*.

Babies have more SC tissue than preschool children. Children from 2 to 6 years have very little SC tissue regardless of gender. Children from 7 to 13 years gain SC tissue slowly but SC tissue thickness is almost the same in both genders until puberty. At puberty, girls increase their SC tissue more rapidly than boys as a result of hormonal differences.

SC tissue thickness when combined with the currently available needle lengths yields a relatively clear indication of the risk of IM injection. **Tables 1** and **2** show the risks for adult and pediatric persons with diabetes, respectively. It is clear from these data that the shorter the needle, the lower the risk of IM injection.

5. IM insulin

IM-injected insulins have a much greater variability in absorption and effect (PK and PD) compared to SC-injected. This variability is influenced by both exercise and the properties of the individual insulins. Human insulins and the new analogs also differ as to their PK when injected IM. In general, IM insulin is often associated with a more rapid absorption and unexplained hypoglycemia [17–19]. Because of the difficulty of predicting the impact of IM injections on PK and PD, various measures can be taken to avoid injecting IM: using of shorter needles, lifting of a skin fold into which one injects the insulin, or choosing injection sites with thicker layers of SC fat. A combination of the above techniques can also be used [20].

6. Needle length

In the last decade, insulin needle lengths have decreased dramatically. Previously, adults were given needles that were ≥ 8 mm long and children ≥6 mm. As shown in **Tables 1** and **2**, these lengths are now universally recognized as too long. They make IM injections more likely, and on the whole, the length of the needle has little or nothing to do with glucose control, according to a multitude of studies [8, 21–28]. Longer needles also tend to have larger diameters (smaller G or gauge), which correlates with a greater injection pain.

Hirsch [8] compared the 4-mm pen needle to 5- and 8-mm needles and showed the former to be safe and efficacious in adults (i.e., comparable glucose control); leakage from the skin was equivalent and both pain scores and overall preference were better with the 4 mm. In Japan, Miwa [29] compared the 4-mm needle with 6 mm and showed equivalent results, as did Nagai [30] when comparing 4-to 5-mm pen needles. Hirose [31] found equivalent modeled PK/PD results for the 4 mm compared to the 6- and the 8-mm needles, in young non-diabetics. Birkebaek [32] found a reduced IM risk with 4 versus 6-mm PNs in children and lean adults. Lo Presti [14] measured the skin and SC in children and adolescents with diabetes (ages 2–17) and concluded that the safest needle length for all ages is the 4 mm.

In obese adults, Bergenstal [33] recently showed that the 4-mm pen needles deliver equivalent glycemic control (HbA1c) to both 8- and 12.7-mm pen needles. These obese patients were taking

relatively high doses of glargine (>40 IU), with total daily dose (TDD) insulin up to 300 U daily. No differences between 4- and both 8- and 12.7-mm PNs in hypo- or hyperglycemic events or insulin leakage were found in obese subjects with BMI up to nearly 60 kg/m^2. The 4-mm needle was found to be less painful, easier to use, easier to insert, and less anxiety-provoking than 8 or 12.7 mm (all at $p < 0.05$).

Based on these studies, FITTER recommended the following:

- The 4-mm needle inserted perpendicularly is long enough to penetrate the skin and enter the subcutaneous tissue, with little risk of intramuscular (or intradermal) injection. Therefore, it should be considered the safest pen needles for adults and children regardless of age, gender, ethnicity, and BMI. **A1**
- The 4-mm needle should be inserted perpendicular to the skin (at 90° to the skin surface), not at an angle, regardless of whether a skin fold is raised. A1.
- Very young children (6 years old and under) and very thin adults should use the 4-mm needle by lifting a skin fold and inserting the needle perpendicularly into it. Others may inject using the 4-mm needle without lifting a skin fold. A1
- Patients with tremors or other disorders, which make them unable to hold a 4-mm pen needle in place, may need longer needles. B3

7. Injection site care

Recommended injection sites include the abdomen, lateral thigh, arms, and buttocks [34–38]. In the abdomen, injections or infusions in adults may be given within the following boundaries: 1 cm above symphysis pubis, 1 cm below the lowest rib, 1 cm away from the umbilicus, and laterally at the flanks. In the lateral thighs, patients should use the upper third anteriorly. The posterior lateral aspect of the upper buttocks and flanks may be used. In the arm, one may use the mid-third posterior aspect. In children, the abdominal boundaries are similar to adults, but 2 cm is used instead of 1 cm for all distances. A degree of clinical judgment must be used in all cases, adult and pediatric.

8. Human insulin

Soluble human insulin (e.g., regular insulin) has a slower absorption profile than the rapid-acting analogs (lispro, aspart, and glulisine). The PK and PD of regular insulin, as well as those of neutral protamine Hagedorn (NPH), are highly dependent on the body site injected and the technique used. FITTER recommendations state that:

- IM injections of NPH and long-acting insulin analogs must be strictly avoided due to the risk of hypoglycemia [17, 39–41]. **A2**

- The abdomen is the preferred site for soluble human insulin (regular), since absorption of this insulin is fastest there [35, 42–46]. **A1**
- The regular/NPH mix should be given in the abdomen to increase the speed of absorption of the short-acting insulin in order to cover postprandial glycemic excursions [18]. **A1**
- If there is risk of nocturnal hypoglycemia, NPH- and NPH-containing mixes given in the evening should be injected into the thigh or the buttock as these sites have slower absorption of NPH [38, 47, 48]. **A1**

9. Insulin analogs

There are fewer studies of optimal delivery methods for the newer insulin analogs and GLP-1 s. However, insulin analogs are *not* as dependent on injection sites as are human insulins or NPH. From the existing studies, FITTER recommended the following:

- Rapid-acting insulin analogs may be given at any of the injection sites, as absorption rates do not appear to be site-specific [49–53]. **A2**
- Rapid-acting analogs should not be given IM although studies have shown that absorption rates are similar from fat tissue and resting muscle. Absorption from working muscle has not, however, been studied [50, 51, 54]. **A2**
- Pending further studies, patients may inject long-acting insulin analogs in any of the usual injecting sites, with appropriate technique to prevent IM injection which can lead to profound hypoglycemia [55]. **B2**

10. GLP-1 agents

- Pending further studies, patients using non-insulin injectable therapies should follow the recommendations already established for insulin injections with regards to needle length, site selection, and site rotation [56–58]. **A2**

11. Lipohypertrophy

LH is the most common complication of insulin injection [59–62] or infusion [63, 64], with prevalence rates of 50% or higher. Risk factors for LH appear to be longer time on insulin, more daily injections, failure to carefully rotate injection sites, and extensive reuse of needles [59, 65–68]. The latter two risk factors are modifiable. Insulin injected into LH has been reported to have delayed or erratic absorption which may worsen glucose control, although these trials are older with less rigor, less precise insulin assays, or very small sample sizes

which in one case led to a conclusion that injecting into LH did not worsen inherent variability of insulin uptake [69–72]. A crossover glucose clamp study [73] showed that both insulin absorption and action when injected into LH are blunted and are 3–5X more variable than when the same insulin dose is injected into non-LH areas. A controlled mixed-meal tolerance test in the same study also showed a reduced insulin absorption, and prolonged postprandial hyperglycemia when the insulin was injected into the LH area. When patients change from delivering insulin into LH and move to normal tissue, they are at risk of hypoglycemia and must lower their doses. Gentile [74, 75] has shown convincingly that HCPs trained to detect LH can do so with extremely high efficiency using the physical examination alone, achieving up to 97% consistency levels. FITTER issued the following recommendations:

- Switching injections from lipohypertrophy to normal tissue often requires a decrease in the dose of insulin injected. The amount of change varies from one individual to another and should be guided by frequent blood glucose measurements. Reductions often exceed 20% of their original dose [66, 76]. **A1**
- Injections should be systematically rotated in such a way that they are spaced at least 1 cm (or approximate width of an adult finger) from each other in order to avoid repeat tissue trauma. **A2**
- One scheme with proven effectiveness involves dividing the injection site into quadrants (or halves when using the thighs or the buttocks), using one quadrant per week and moving quadrant to quadrant in a consistent direction (e.g., clockwise) [77]. **A3**

A multicenter interventional study in the UK [78] showed that education focused on these recommendations resulted in significantly reduced clinically detectable LH after 6 months, with LH either disappearing completely or decreasing by approximately 50% from its original size. The mean HbA1c fell by more than 4 mmol/L, and there were significantly reduced levels of unexpected hypoglycemia and glycemic variability. The mean TDD of insulin in the study population fell by an average of 5.6 IU by study close.

In a controlled, prospective, multicenter study in French patients [79], all of whom had LH, the intervention consisted of instructions to move injections to non-LH areas, to correctly rotate within injection sites, to forego needle reuse, and to switch to 4-mm needles in order to facilitate correct rotation without increased IM injections. These patients were also given intensive education on the injection recommendations as summarized in this chapter. Control patients were informed of the presence of LH and were told that injections should not be given into LH. They received usual and standard education. In the intervention group, there was a significant decrease of TDD of insulin of approximately 5 IU versus baseline ($P = 0.035$). There were significant decreases in HbA1c (up to 0.5%) in both intervention and control groups, with no significant differences between groups. A significant number of intervention patients improved their IT habits. The authors concluded that the intervention was effective in both groups, but that intensive education in LH management yielded more rapid and superior outcomes.

An interventional study in Moscow [80] followed three groups of T1DM and T2DM patients for 6 months. Two groups received structured injection training (with one group receiving 4-mm needles for each injection while the other did not) and a control group which did not get training or needles. Both training groups had HbA1C reductions of approximately 1% but the non-training group saw no change. Needle reuse and LH declined in the training groups and injection technique improved but none of these changes were seen in the non-training group.

The available data from intervention trials in patients with insulin-related LH show consistently positive outcomes. However, there are limitations to each trial—some were not randomized; in another, the control group received meaningful parts of the educational intervention [79]. Results of one or more ongoing randomized clinical trials should provide more definitive answers to the impact of injection technique training in the near future.

12. Needle reuse

Reusing needles is a common practice of injecting patients, mainly for reasons of convenience and cost-saving. However, a number of studies have linked needle reuse to LH [59, 65, 66, 81–83], especially when the reuse is excessive (≥5 times/needle). Injection pain was associated with reuse in one study [84] although another one disputed these results [85]. Another study found bacterial growth on reused needles and inflammatory changes (skin redness) at injection sites of patients who reused needles [86, 87]. Although local infections or abscesses have not been reported with needle reuse, FITTER recommends against reusing needles, which are labeled by regulatory agencies for single use.

13. Safety

Patients should never share insulin pens, whether in the hospital or at 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 the next user. Sonoki [88] found hemoglobin in a number of cartridges which patients had used only once. Le Floch [89] also studied the contamination of cartridges after one use and found similar findings. A recent US study corroborated these findings [90]. The rule with insulin injections is clear: one patient/one insulin pen.

Insulin needles are the most commonly used sharp worldwide. If not disposed of properly, needle-stick injuries with used insulin needles could transmit hepatitis, HIV, or other blood-borne pathogens. This is a major public health issue. Technologies exist to minimize this risk. FITTER recommended the following to minimize the risk of needle-stick injuries, particularly in a hospital or other inpatient setting:

- Safety-engineered devices play a critical role in protecting injectors, pump users, and downstream workers [91]. **A1**
- Needle recapping should not be done. **A2**
- Sharp containers must be easily accessible at the point of care beside the patient, prior to the injection or infusion. **A2**
- Safe disposal should be taught to patients, caregivers, and all others who may come in contact with the sharp device from the beginning of injection or infusion therapy and reinforced throughout [92] **A2**
- Under no circumstance should sharps material be disposed of into the public trash or rubbish system. **A3**

14. Insulin infusion

Continuous subcutaneous insulin infusion (CSII) has been used for 40 years [93, 94]. Insulin infusion sets (IISs) deliver insulin into the SC, and they have been associated with numerous adverse side effects [95]. It is generally agreed that if a patient has otherwise unexplained hyperglycemia, they should administer a correction bolus via their pump. If the blood glucose does not decline at least 50 mg/dL by 90 min, they should (1) remove the set, (2) give a correction with a pen or a syringe, and (3) insert a new set. FITTER recommended the following additional recommendations for CSII and IIS users:

- CSII cannula should be changed every 48–72 h in order to minimize infusion site adverse events and potential metabolic deterioration. However, these times are very patient-dependent and should be adjusted accordingly. **A1**
- All CSII patients should be taught to rotate infusion sites along the same principles that injecting patients are taught to rotate injection sites. **A1**
- Any CSII patients with unexplained glucose variability including frequent hypoglycemia/hyperglycemia should have infusion sites checked for lipohypertrophy, nodules, scarring, inflammation, or other skin and SC conditions that could affect insulin flow or absorption. **A1**

15. Conclusion

Insulin has a very low therapeutic index. The margin between its greatest therapeutic benefit and its unacceptable side effects is low. Without careful attention to optimal insulin delivery, patients can find themselves on either side of a slippery slope: either suboptimal therapeutic benefit or high toxicity. Optimal insulin delivery is complex and involves choices that

patients and professionals may not have previously considered: the choice of injection sites as a function of the insulin delivered, the choice of needle length as a function of SC thickness, the injection or infusion technique which ensure consistently effective SC delivery, the precise and systematic rotation of delivery sites, reduced or non-reuse of sharps, and safe disposal of used sharps which reduces needle-stick injury risk to family members or the community at large [96]. We have provided both evidence-based recommendations and proof that these work in practice and deliver insulin with an improved therapeutic index and better outcomes—both clinical- and patient-reported. The challenge now is to scale these recommendations so that all insulin-using patients and insulin-prescribing professional know and follow them.

Conflict of interest

Authors KS and LH are employees of BD, a manufacturer of injecting devices. All other authors declare that they have no conflict of interest.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Abbreviations

BMI	body mass index
CSII	continuous subcutaneous insulin infusion
DKA	diabetic ketoacidosis
FIT	Forum for Injection Technique
FITTER	Forum for Injection Technique and Therapy: Expert Recommendations
G	gauge (of needle).
GCP	good clinical practice.
GLP-1	glucagon-like peptide-1 receptor agonists

HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
ID	intradermal
IM	intramuscular
ITQ	injection technique questionnaire
IU	international unit (of insulin)
LH−	patient without lipohypertrophy
LH	lipohypertrophy
LH+	patient with lipohypertrophy
NPH	neutral protamine hagedorn (also known as insulin N)
NSI	needle-stick injury
PD	pharmacodynamics
PK	pharmacokinetics.
SC	subcutaneous
T1DM	type 1 diabetes
T2DM	type 2 diabetes.
TDD	total daily dose (of insulin)

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