CLOSER LOOK

MEMORANDUM

Mayo Clinic Proceedings publishes FITTER Forward Expert Recommendations on insulin injection technique – April 2, 2025

Executive Highlights

- ***Mayo Clinic Proceedings*** **published the Forum for Injection Technique and Therapy Expert Recommendations (FITTER) Forward Expert Recommendations for insulin injection technique,** the first update to FITTER's recommendations in nearly a decade. The updated recommendations paper builds upon the extensive guidance offered in prior publications and is authored by 16 leaders in the diabetes field – Dr. David Klonoff (Mills-Peninsula Medical Center), Ms. Lori Berard (Pink Pearls, Canada), Dr. Denise Reis Franco (Centro de Pesquisas Clínicas, Brazil), Prof. Sandro Gentile (Campania University "Luigi Vanvitelli", Italy), Dr. Olga Victoria Gomez (Instituto Global de Excelencia Clínica Keralty, Colombia), Dr. Zanariah Hussein (Hospital Putrajaya, Malaysia), Dr. Akshay B. Jain (University of British Columbia, Canada), Dr. Sanjay Kalra (Chandigarh University, India), Dr. Henry Anhalt (embecta), Prof. Julia K. Mader (Medical University of Graz, Austria), Dr. Eden Miller (St. Charles Hospital), Dr. Miguel Augusto O'Meara (Universidad del Rosario, Colombia), Ms. Michelle Robins (Northern Health, Australia), Prof. Felice Strollo (IRCCS San Raffaele Pisana, Italy), Dr. Hirotaka Watada (Juntendo University Graduate School of Medicine, Japan), and Prof. Lutz Heinemann (Science Consulting in Diabetes GmbH, Germany).
- **The recommendations include** the best practices for insulin pen component selection, injection procedures, lipohypertrophy risk reduction, and patient and healthcare provider (HCP) education. Some key recommendations include:
  - All individuals should use 4-mm needle insulin pens and 6-mm needle syringes as available;
  - Skin lifts should be performed in certain patient populations;
  - Injection sites should be systematically rotated;
  - Needles should not be reused unless limited by resources; and
  - When available, ultrasound detection of lipohypertrophic sites is now recommended, which may improve sensitivity and objectivity compared to palpation and visual examination.
- **The recommendations aim to support providers and people with diabetes in maximizing insulin's effects and optimizing delivery method.** When discussing the initiation of insulin therapy, HCPs should identify clinical, emotional, and social needs and personalize insulin delivery devices accordingly.

Table of Contents

Section 1: Insulin injection device recommendations and techniques

The FITTER Forward Expert Recommendations issued guidance for optimal use of insulin injectors, which included tips for those using injections.

- **Needle length:** The recommended needle length is 4 mm for all individuals, regardless of age or BMI. 3.5-mm needles are also effective but are only used in select international markets. 5-mm pen needles may be applicable as a backup option. Pen needles longer than 5 mm are not recommended for any populations – aside from efficacy and comfort being major priorities, longer needles, as we understand it, can increase the risk of intramuscular injection, which can lead to variable blood glucose levels and other complications, especially in those with less subcutaneous fat.
- **Skin lift:** To minimize the risk of unintentional intramuscular injection, a skin lift may be necessary for certain populations. A skin lift is defined by the authors as a "'pinch up' technique to accumulate sufficient subcutaneous tissue for injections." The authors recommend the following populations should consider this technique:
    - Older adults (over 60, for example)
    - Individuals with low BMI (<19 kg/m^2) using 4-mm pen needles
    - Pregnant women, who should use either lateral abdominal areas or a skin lift in central areas overlying the fetus in the second trimester. Both techniques can be used in the third trimester. We wonder about the degree to which they are taught this or will learn about it
    - Children using 4-mm pen needles. Of note, syringes are ideally recommended against for children under the age of six years, as even the shortest syringe is still longer than a pen needle, though we understand that is not possible for all.
- **Pen gauge:** A 32-gauge pen needle is recommended. Higher gauges are more comfortable for most patients. As a sidenote, we believe a high number of people reuse pen needles, though we also think that there is lots of information out there to prompt fewer people to do this – fair warning, but readers that would like to learn more on needle reuse for insulin can see more at this Reddit forum. Overall, there is lots of negativity associated with it outside affordability.
- **Pen base design:** The design of pen bases can affect injection technique. The ideal base should not "indent" the skin during injection. Pens with posted bases have a smaller surface area, which may lead to excessive force during injection – the most commonly reported injection technique error in a survey of 230 people with diabetes in Canada – see "Insulin Injection Practices in a Population of Canadians with Diabetes: An Observational Study" by Dr. Lori Berard, et. al. We are interested in learning more from patients about injections and will be back after checking with dQ&A.

Section 2: Insulin storage, injection procedures, and post-injection practices

The FITTER report outlines several evidence-based practices for insulin storage and injection procedures, much of which remains the same compared to the 2016 report.

- **Insulin storage:** While refrigeration appears to be key to insulin's stability in storage, some recommendations were made to increase comfort of injection.
    - **Unopened insulin vials** should be refrigerated at 2-8°C (36-46°F).
    - **Open insulin vials** should be stored at ambient temperatures of 15-30°C (59-86°F), away from direct sunlight.
    - **Insulin should be removed from the refrigerator 30 to 60 minutes prior to injection** to reduce pain and risk of lipodystrophy.
- **Injection sites:** Recommended sites include the abdomen, thigh, buttock, and upper arm. The upper arm is the least preferred due to difficulty in injecting at a 90° angle or performing an effective skin lift. Sites of lipohypertrophy, scars, tattoos, and skin lesions should be avoided to reduce the risk of impaired insulin

absorption. As a sidenote, impaired insulin absorption is challenging to identify – many patients may "think" they have done something wrong and have too much hyperglycemia (as one example) when in fact, the high blood glucose often reflects other problems, such as lipohypertrophy.

    - **Injection site rotation.** To prevent lipodystrophy, it is recommended to systematically rotate the injection site. Lipodystrophy is a skin complication that is the result of repeating injection/infusions of insulin into the same site. To prevent it, the body should be divided into quadrants; the injection quadrant should be rotated every three to four days. Each injection should be at least 1 cm away from previous sites. Providers should review rotation practices annually and when signs of lipodystrophy appear (see more below).

- **Injection technique for pens and syringes:** The recommended technique for syringes was unchanged from the 2016 FITTER guidelines. Clinicians should continue to educate patients on syringe components, safety, and efficacy. Patients should also understand how to select the appropriate syringe size based on insulin doses. The report suggests using 6-mm syringe needles with 1 mL, 0.5 mL, and 0.3 mL syringes for U-100 insulin doses of ≤100, 50, and 30 units, respectively. Patients should also be trained to prevent vacuum formation and remove air bubbles when drawing insulin. For pen injections, the following procedure is recommended.

    1. Assemble the pen with the needle, prime it according to manufacturer instructions, and select the needle size in accordance with the above recommendations.
    2. Select the injection site, in accordance with the above recommendations on site rotation.
    3. Apply steady, even pressure on the dose button until the injection is complete and cues are received, such as the dose dial returning to zero.
    4. Remove the needle after at least 3 seconds, ideally after 10 seconds.

- **Post-injection practices:** Reusing needles is not recommended due to the risk of infection and pain from needle blunting. Despite this, many people with diabetes worldwide reuse needles due to resource limitations. While evidence on the maximum number of uses is limited, it's suggested that pen needles can be used up to five times without significantly increasing pain.
- **Non-insulin injectable therapies:** The same injection practices for insulin can be applied to non-insulin injectables, like incretin therapies, to lower risk of lipohypertrophy.

Section 3: Proactive risk reduction and detection of lipodystrophy

The guidance also included recommendations to reduce risk for lipodystrophy, which includes lipohypertrophy, lipoatrophy, and amyloidosis. In addition to physical discomfort, lipodystrophy can impair insulin absorption, which can increase glucose variability and the risk for hypoglycemia or hyperglycemia. The publication provided the following guidance for lipohypertrophy detection, monitoring, and prevention:

- **Detection:** Lipohypertrophy screening should be a routine part of diabetes-related complication assessment due to its high prevalence, occurring in 37-64% of adults with diabetes on insulin therapy. When available, ultrasound screening for lipohypertrophic sites is recommended, an update from 2016 guidance. This method may improve sensitivity and objectivity compared to palpation. However, if availability and cost are a concern, structured and periodic palpation and visual examination should still be performed. This may be conducted as self-examination or by HCPs. The document emphasizes that simply asking patients about site rotation is insufficient – some form of examination is needed to confirm site rotation.

    - **Once lipohypertrophy is detected,** PWD should cease injecting into those sites. Discussions should center on risk reduction by regularly rotating sites, avoiding the delivery of cold insulin, and avoiding needle reuse.

- **Monitoring:** Documenting lipohypertrophy with visuals may be helpful to track improvement over time. In skilled nursing facilities, site documentation is recommended to assist with regular rotation.
- **Treatment:** Sites with lipohypertrophy tend to decrease in size when rotation is implemented. Anti-inflammatory approaches such as glucocorticoid injections, low-dose oral prednisone, or cromolyn sodium

may also improve the sites. In extreme cases, liposuction may also be considered.

    - **Using rapid-acting insulin analogues** for prandial injections may be advantageous. These analogues provide faster absorption from insulin depots, which reduces the local interaction of insulin with adipocytes.

Section 4: Structured injection training to optimize outcomes

The publication includes a new section with recommendations for maximizing insulin's action. When discussing the initiation of insulin therapy, HCPs should identify unique needs and personalize insulin delivery devices to reduce anxiety. Evidence-based educational strategies to provide the best outcomes are as follows:

- Provide early education on insulin injection and devices in newly diagnosed PWD, whether insulin therapy is initiated at the time of diagnosis or not
- Understand patients' treatment needs, access barriers, preferences, and concerns
- Discuss the "why" behind all recommendations and use visual illustrations
- Explain warning signs that should be mentioned to HCPs, such as unusual pain, bleeding, bruising, or excessive force required for injection
- Assess understanding by asking patients to demonstrate the correct technique after instruction
- Provide ongoing assessment, refresh education, and ensure clinician accessibility to positively influence treatment adherence
- Ensure all clinic staff are familiar with new insulin delivery technology and educational strategies

HCPs are also advised to review CGM data to monitor for glycemic changes, assuming patients have access t. Unexplained changes in glucose levels or Time in Range could suggest injections are being performed into areas with lipohypertrophy or are otherwise administered incorrectly. As we learned from Post-DERMIS 2024, inflammation is positively associated with insulin dose (i.e., larger doses are needed when inflammation is present) and negatively associated with Time in Range.

Section 5: Future perspectives and conclusions

The authors acknowledged that resource constraints around the world may limit implementation of the FITTER recommendations. Therefore, the authors encourage HCPs, authorities, payers, and manufacturers alike to support equitable resource allocation.

- **Future reports will include separate recommendations for new innovations,** such as needle-free injectors, inhaled insulin, patch pumps, and more. The authors note that the technology landscape has significantly evolved since the 2016 report, which only covered conventional tubed insulin pumps with infusion sets.
- **All diabetes stakeholders can assist efforts to reduce the environmental waste of devices.** For instance, manufacturers should prioritize green device designs, regulators should establish sustainability standards, and HCPs should promote recycling programs for eligible materials.
- **This work aims to inspire more research on optimal injection technique education.** Manufacturers should add key education points to their instructions and PWD can tell their HCPs which education programs are most helpful to them.

The report emphasizes insulin will have limited and/or unpredictable effects if not delivered properly. HCPs, PWD, and caregivers must therefore prioritize injection technique education to improve clinical outcomes and reduce healthcare costs. The authors called for more research on optimal injection technique education and recommended that device manufacturers include education material in training manuals.

Insightful commentary from Dr. David Klonoff

"Many people with diabetes depend on insulin. Proper injection techniques for this powerful medication can maximize predictable glycemic responses, improve effectiveness, and minimize adverse side effects. The FITTER Forward report

was developed by an international panel of 16 diabetes experts from13 countries to address proper insulin injection techniques, and their impact on achieving glycemic goals. The report also addresses the science behind needle structure, proper insulin storage, needle disposal, the prevention and detection of lipohypertrophy, and structured education programs tools for principles of injection. This report is an updated version of a prior expert report published nine years ago. The science of insulin injection has advanced considerably since then, especially in understanding the causes and treatments of lipohypertrophy, which can present with palpable or visible-with-ultrasound areas of fat necrosis along with pain, new onset lack of pain, leaking, bleeding, or bruising, or a need for increased force. FITTER Forward addresses how to inject properly to prevent the complications of insulin injection."

--by Nour Khachemoune, Jeremy Alkire, Andrew Goyette, Elaine Young, Monica Oxenreiter, and Kelly Close