

New injection recommendations for patients with diabetes

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Abstract

Aim: Injections administered by patients are one of the mainstays of diabetes management. Proper injection technique is vital to avoiding intramuscular injections, ensuring appropriate delivery to the subcutaneous tissues and avoiding common complications such as lipohypertrophy. Yet few formal guidelines have been published summarizing all that is known about best practice. We propose new injection guidelines which are thoroughly evidence-based, written and vetted by a large group of international injection experts.

Methods: A systematic literature study was conducted for all peer-reviewed studies and publications which bear on injections in diabetes. An international group of experts met regularly over a two-year period to review this literature and draft the recommendations. These were then presented for review and revision to 127 experts from 27 countries at the TITAN workshop in September, 2009.

Results: Of 292 articles reviewed, 157 were found to meet the criteria of relevance to the recommendations. Each recommendation was graded by the weight it should have in daily practice and by its degree of support in the medical literature. The topics covered include The Role of the Professional, Psychological Challenges, Education, Site Care, Storage, Suspension and Priming, Injecting Process, Proper Use of Pens and Syringes, Insulin analogues, Human and Pre-mixed Insulins, GLP-1 analogs, Needle Length, Skin Folds, Lipohypertrophy, Rotation, Bleeding and Bruising, Pregnancy, Safety and Disposal.

Conclusion: These injecting recommendations provide practical guidance and fill an important gap in diabetes management. If followed, they should help ensure comfortable, effective and largely complication-free injections.

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Keywords: diabetes mellitus, treatment, insulin, insulin therapy, GLP-1 analogs, injections, needles, subcutaneous tissue, lipohypertrophy, complications, technical aspects, review, recommendations.

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Résumé

Nouvelles recommandations pour les injections chez les patients diabétiques

Objectif : Les injections que réalisent les patients atteints de diabète sont l'un des piliers de la gestion de la maladie. Une bonne technique d'injection est essentielle pour éviter les injections intramusculaires, pour délivrer le produit injecté de manière appropriée aux tissus sous-cutanés et pour éviter les complications courantes telles que la lipohypertrophie. Pourtant, peu de recommandations officielles résumant tout ce qui est connu des meilleures pratiques ont été publiées. Nous proposons des nouvelles lignes directrices concernant les injections, fondées sur des preuves publiées et validées par un large groupe d'experts internationaux.

Méthodes : Une étude systématique de toutes les études et publications qui portaient sur le thème des injections chez les diabétiques a été effectuée. Un groupe d'experts internationaux s'est réuni régulièrement durant deux ans pour examiner ce projet et rédiger des recommandations. Celles-ci ont ensuite été soumises pour examen et révision à 127 experts de 27 pays lors de l'atelier TITAN en Septembre 2009.

Résultats : Sur les 292 articles examinés, 157 ont été jugés conformes aux critères de pertinence pour les recommandations. Chaque recommandation a été classée selon l'importance qu'elle devait avoir dans la pratique quotidienne et par son niveau de preuve dans la littérature médicale. Les sujets abordés comprennent le rôle des professionnels de santé, les aspects psychologiques des injections, l'éducation, la préparation du point d'injection, le stockage et la remise en suspension de l'insuline, les étapes de l'injection, l'utilisation correcte des stylos et des seringues, les analogues de l'insuline, les insulines humaines et les insulines pré-mélangées, les analogues de GLP-1, la longueur de l'aiguille, le pli cutané, les lipohypertrophies, la rotation des points d'injection, les hématomes et les saignements, la grossesse, la sécurité des soignants et l'élimination des déchets.

Conclusion : Ces recommandations et ces conseils pratiques qui concernent les injections comblent une lacune importante dans la prise en charge du diabète. Si elles étaient suivies, elles devraient contribuer à assurer des injections confortables, efficaces et la plupart du temps dénuées de complications.

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Mots clés : diabète, traitement, insuline, insulinothérapie, analogues du GLP-1, injections, aiguilles, tissu sous-cutané, lipohypertrophie, complications, aspects techniques, revue générale, recommandations.

1. Introduction

This paper presents new injection recommendations for patients with diabetes based on the latest studies and publications in the field. While much attention has been paid to the pharmacokinetic and pharmacodynamic properties of diabetes therapies, not enough is given to achieving the most comfortable, consistent subcutaneous (SC) delivery of the injected medication. Correct injection technique is critical for optimal control of diabetes.

In recent years there has been a major shift towards shorter-length needles as studies proving their safety, efficacy and user preference have been published [1,2], presentations given at meetings [3,4] and guidelines issued [5-8]. Clear recommendations regarding the use of such needles in specific patient populations have however been lacking. This paper attempts to provide such guidance. In addition, these recommendations cover issues not previously addressed, such as psychological barriers to insulin therapy, appropriate injection technique with the newer insulin analogues and GLP-1 agents, and the prevention of injecting complications such as needle stick injuries and lipodystrophy [6-8].

The new recommendations were informed by the results of the second Injection Technique Questionnaire (ITQ) survey. Over 8 months, from September 2008 to June 2009, more than 4300 insulin-injecting patients with diabetes from 171 centers in 16 countries participated in the survey, making it

one of the largest multi-center studies of its kind in diabetes. The results of this survey had just become available as the new recommendations were being formulated.

The survey results and an initial draft of the new recommendations were presented at the Third Injection Technique workshop in Athens (TITAN) held in Athens, Greece, on 10-13 September, 2009, at which 127 doctors, nurses, educators and psychologists from 27 countries (see Appendix) met to discuss and debate these proposals. The new recommendations were significantly reshaped by the collective input of this group.

2. Methods and Materials

An international group of experts in injection technique (see list of authors and Appendix) met regularly over an 18-month period, including at the TITAN workshop. The present work is based on their review and analysis of all peer-reviewed studies and publications which bear on the subject of injections in diabetes. Articles were searched using Pub Med, Medline and Cochrane Controlled Trials. The search spanned the time period of 1980 through the present and used the terms *insulin*, *subcutaneous injections*, *insulin injections*, *injection technique* and *glucagon-like protein 1* (GLP-1). Specifically targeted were randomized controlled trials related to insulin delivery into SC, and intramuscular (IM) tissues, anatomic studies of

the skin and SC tissue compartments, and pharmacokinetic studies of insulin injected at the usual injecting sites and into specific tissues; also included were reviews and published guidelines focused on best practice in insulin injection. Three authors (KS, CL and AF) reviewed and selected articles. Of 292 reviewed, 157 were found to meet the criteria of relevance to the recommendations.

The panel decided that for the strength of a recommendation the following scale would be used:

- A. Strongly recommended
- B. Recommended
- C. Unresolved issue.

For the scientific support we use this scale:

- 1. At least one randomized controlled study
- 2. At least one non-randomized (or non-controlled or epidemiologic) study
- 3. Consensus expert opinion based on extensive patient experience.

Thus each recommendation is followed by both a letter and number (e.g. A2). The letter indicates the weight a recommendation should have in daily practice and the number, its degree of support in the medical literature. The most relevant publications bearing on a recommendation are also cited. There are comparably few randomized clinical trials in the field of injection technique (compared, for example, with blood pressure control) so judgments such as 'strongly recommended' versus 'recommended' are based on a combination of the weight of clinical evidence, the implications for patient therapy and the judgment of the group of experts. Where no clinical trials evidence exists, but experience is significant and compelling, the section has been entitled 'Observations' and no grading scheme has been applied. For each topic a section of background and introductory information appears first, followed by the actual recommendations in shaded blocks of text.

These recommendations apply to the majority of injecting patients, but there will inevitably be individual exceptions for which these rules must be adjusted.

3. The New Injection Recommendations

3.1. The Role of the Health Care Professional

There are currently three classes of injectable medications available for diabetes therapy: insulin, GLP-1 agents and amylin analogue [9-11]. The health care professional plays a crucial role in the optimal use of these agents. Proper injection technique by patients is essential for achieving good diabetes management, reducing absorption variability and attaining optimal drug effect [10-16].

Observations

- Key tasks of the health care professional (HCP) include teaching patients (and other care-givers) how to inject correctly and addressing the many psychological

hurdles the patient may face when injecting, especially at the initiation of such treatment.

- The HCP must have an understanding of the anatomy of injection sites in order to help patients avoid IM injections and ensure that injections are consistently given into the SC tissue, without leakage/backflow or other complications.
- In addition, the HCP must have knowledge of absorption profiles from different tissues of the injected agents.

3.2. Psychological Challenges of Injections

3.2.1. Children

For the purpose of these recommendations, childhood is defined as birth to the onset of puberty. Children (and their parents) are often very anxious when starting insulin therapy. This anxiety often relates to earlier experiences of pain with immunizations as well as negative societal messages regarding injections [17]. Additionally HCPs and parents fear hurting children and often transmit their own anxieties. Anticipatory fear is often worse than the actual experience of the injection. Fear and anxiety can be significantly relieved by having the child and parent give themselves an injection of saline, insulin diluent or one unit of insulin early on after their diagnosis of diabetes. Often they are surprised at how painless (or relatively so) the injection is. Parents who are well-prepared beforehand will transmit less anxiety to their children. In fact the presence of a calm and reassuring parent is the most effective support for a distressed child [18-19].

Recommendations

- Younger children may be helped by distraction techniques (as long as they do not involve trickery) or play therapy (e.g. injecting into a stuffed animal) while older children respond better to cognitive behavioral therapies (CBT). [19] A2
- CBT include relaxation training, guided imagery, graded exposure, active behavioral rehearsal, modeling and reinforcement as well as incentive scheduling. [19] A2
- Children have a lower threshold for pain than adults and sometimes find injecting uncomfortable. The HCP should ask about pain, since many young patients may not bring it up spontaneously. [18, 20] A2
- Use of indwelling catheters and injection ports (e.g. Insufion®, I-port®) at the beginning of therapy can help reduce fear of injections and associated pain, and may improve adherence to multiple daily injection regimens. [21-25] B1

3.2.2. Adolescents

For the purpose of these recommendations, adolescence

is defined as puberty through 18 years of age. HCPs should recognize that many adolescents struggle with issues surrounding insulin and most are reluctant to inject in front of peers. There is a greater tendency among adolescents to skip injections, often because of simple forgetfulness, although at other times this may be due to peer pressure, rebellion, pain, etc [17]. Some adolescents associate insulin with weight gain and HCPs should be aware that skipping injections may be used, especially by girls, as a method of losing weight.

Observations

- Adolescents should be reassured that no one manages diabetes perfectly all the time and that occasional slip-ups, as long as they do not become habitual, are not signs of failure.
- Any steps which enhance the adolescent's sense of control (e.g. flexible injection schedule for weekends and holidays) will have positive consequences.
- Skipping injections to lose weight should be actively investigated whenever there is a discrepancy between the insulin doses reported and blood glucose readings or when one finds unexplained weight loss.
- All patients, but especially adolescents, should be encouraged to express their feelings about injecting, particularly their frustrations and struggles.

3.2.3. Adults

Few prospective studies have been published, but the theme of psychological insulin resistance (on the part of both patients and HCPs) is being increasingly debated [26-31]. Very few adults have true needle phobia (a paralyzing fear of needles) but many have anxiety about injecting, especially at the beginning of therapy [26, 27]. This anxiety can be somewhat relieved, starting at the time of diagnosis, by the demonstration of a self-injection of saline/diluent by the HCP and then by the patient. However, even experienced patients may view injections with a degree of regret and loathing [28, 29].

Recommendations

- The HCP should prepare all newly-diagnosed patients with type 2 diabetes for likely future insulin therapy by explaining the natural, progressive nature of the disease, stating that it includes insulin therapy and making clear that insulin treatment is not a sign of patient failure [30] A3.
- Both the short- and long-term advantages of good glucose management should be emphasized. Finding the right combination of therapies leading to good glucose management should be the goal, rather than minimizing the number of agents used [31, 32] A3.
- Through culturally-appropriate metaphors, pictures and stories, HCPs should show how insulin injections enhance both the duration and quality of life [31] A2.
- HCPs should reflect on their own perceptions of insulin

therapy and avoid using any terms (e.g. "we may need to put you on the needle")-even casually-which imply that such therapy is a sign of failure, a form of punishment or a threat [33,34] A3.

- In adults, as in all age groups, pen therapy may have psychological advantages over syringe therapy [31, 35-37] A2.

3.3. Therapeutic Education

Studies have shown that not all patients receive education about injections and for those who do, not all essential topics are covered [2,28,29]. Essential topics include:

- the injecting regimen
- the choice and management of the devices used
- the choice, care and self-examination of injection sites
- proper injection techniques (including site rotation, injection angle and possible use of skin folds)
- injection complications and how to avoid them
- optimal needle lengths
- safe disposal of used sharps [32-35,38-41].

Decisions regarding these injection parameters should be made in a discussion context where the patient is a partner and the HCP offers experience and advice [39, 40]. When educating in a group setting, there is evidence that better compliance and lower subsequent HbA_{1c} values are achieved if the HCP has formal training as an educator [42].

Recommendations

- The HCP should spend time exploring patient (and other care-givers') anxieties about the injecting process and insulin itself [33, 40] A3.
- At the beginning of injection therapy (and at least every year thereafter) the HCP should discuss each of the above essential topics and ensure this information has been fully understood [34] A3.
- Current injection practice should be queried and observed, and injecting sites examined and palpated, if possible at each visit but at least every year [38,40,41] A3.
- A quality management process should be put in place to ensure that correct injection technique is regularly practiced by the patient and is documented in the record A3.

3.4. Injection Site Care

Figure 1 shows the recommended injection sites [43-47].

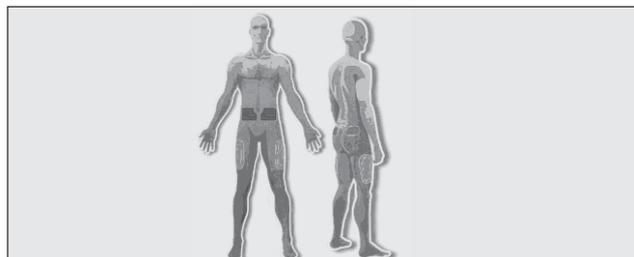


Figure 1. Recommended injection sites.

Injection through clothing has not been associated with adverse outcomes, but the fact that one cannot lift a skin fold or visualize the site when so injecting suggest that this is not optimal practice [48].

Recommendations

- The site should be inspected by the patient prior to injection [5, 6] A3.
- Change sites if the current one shows signs of lipohypertrophy, inflammation, edema or infection [15, 49, 50-55] A2.
- Injections should be given in a clean site using clean hands [56] A2.
- The site should be disinfected when found to be unclean or if the patient is in a setting where infections can be easily spread (e.g. hospital or nursing home) [56] A3.
- Disinfection of the site is usually not required outside the institutional setting [6, 57-60] B2.

3.5. Insulin Storage and Suspension

Most insulin storage data comes from the manufacturers, with few independent studies available. German studies [61-65] have highlighted the previously unappreciated problem of inadequate suspension of cloudy insulins. Some longer-acting insulins contain a predetermined ratio of either crystalline insulin and solvent or crystalline insulin and rapid-acting soluble insulin. The crystalline elements must be resuspended prior to each injection, however patients may be unaware of how best to do this.

Recommendations

- Store insulin in current use (pen, cartridge or vial) at room temperature (for a maximum of one month after initial use, and within expiry date). Store unopened insulin in an area of the refrigerator where freezing is unlikely to occur [66,67] A2.
- Cloudy insulins (e.g. NPH and pre-mixed insulins) must be gently rolled and/or tipped (not shaken) for 20 cycles until the crystals go back into suspension (solution becomes milky white) [61-65] A2.

3.6. Injecting Process

Most insulin injections are not painful, except in the infrequent event that the needle comes into direct contact with a nerve ending. Some patients, however, are exceptionally sensitive to sensations they describe as painful.

Recommendations

- Tips for making injections less painful include:
 - Keeping insulin in use at room temperature;
 - If using alcohol, injecting only when the alcohol has fully dried;
 - Avoid injecting at hair roots;

- Using needles of shorter length and smaller diameter;
- Using a new needle at each injection [5, 6, 17, 36, 68] A2.
- Insert the needle in a quick, dart-like movement through the skin. Inject slowly and ensure that the plunger (syringe) or thumb button (pen) has been fully depressed [69] A3.
- Massaging the site before or after injection may speed up absorption but is not generally recommended [5, 6, 70] C3.

3.7. The Proper Use of Pens

Unlike syringe users, the pen user cannot 'see the insulin going in' when injecting. Obstruction of flow with pens is rare but, when it happens, can have serious consequences.

Recommendations

- Pens should be primed (observing at least a drop at the needle tip) according to the manufacturer's instructions before the injection to ensure there is unobstructed flow and to clear needle dead space. Once flow is verified, the desired dose should be dialed and the injection administered [36, 68] A3.
- Pens and cartridges are for a single patient and should never be shared between patients due to the risk of biological material from one patient being drawn into the cartridge and then injected into another [37,57] A2.
- Needles should be disposed of immediately after use instead of being left attached to the pen. This prevents the entry of air (or other contaminants) into the cartridge as well as the leakage of medication out, which can affect subsequent dose accuracy [71-75] A2.
- Pen needles should be used only once [3, 5, 6, 17, 59, 76, 77] A2.
- After pushing the thumb button in completely, patients should count slowly to 10 before withdrawing the needle in order to get the full dose and prevent the leakage of medication. Counting past 10 may be necessary for higher doses [61,69,71,74,78,79] A1.

3.8. The Proper Use of Syringes

There are regions of the world where significant numbers of patients still use syringes as their primary injecting device. Even in countries where pens are used for most home injections, syringes are still often used in health care settings. In areas where U-40 insulin and U-100 are still on the market together (e.g. Asia, Africa), or where U-500 is used in addition to U-100 (e.g. UK and USA), careful attention must be paid to using the appropriate syringe for each concentration. There is no medical rationale for using syringes with detachable needles for insulin injection. Permanently-attached needle syringes offer better dose accuracy and reduced dead space, allowing the patient to mix insulins if needed. There are currently no

syringes with a needle < 8 mm in length, due to compatibility issues with certain insulin vial stoppers [80].

Recommendations

- When drawing up insulin, the air equivalent to the dose should be drawn up first and injected into the vial to facilitate insulin withdrawal A3.
- If air bubbles are seen in the syringe, tap the barrel to bring them to the surface and then remove the bubbles by pushing up the plunger A3.
- Unlike pens, it is not necessary to hold the syringe needle under the skin for 10 seconds after the plunger has been depressed [69,71,79] A3.
- Syringe needles should be used only once [3, 5, 6, 17, 59, 76, 77] A2.

3.9. Insulin Analogues and GLP-1 agents

Few studies have been done to directly address optimal injection techniques for these newer agents. The recommendations that follow have been extracted from studies addressing the safety, efficacy or pharmacokinetic performance of these agents.

Recommendations

- Rapid-acting insulin analogues may be given at any of the injection sites, as absorption rates do not appear to be site-specific [81-85] A1.
- Rapid-acting analogues 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 [82, 83, 86] A2.
- Pending further studies, patients may inject long-acting insulin analogues in any of the usual injecting sites [87, 88] B2.
- IM injections of long-acting analogues must be avoided due to the risk of severe hypoglycaemia. Patients engaging in athletic activities after injecting long-acting analogues should also be warned about hypoglycaemia [89, 90] A1.
- Pending further studies, patients who inject GLP-1 agents (exenatide, Byetta[®]; liraglutide, Victoza[®]) should follow the recommendations already established for insulin injections with regards to needle length and site rotation [72] A2.
- GLP-1 agents may be given at any of the injection sites as the pharmacokinetics do not appear to be site-specific [91] A1.

3.10. Human insulins

Soluble human insulin (e.g. regular insulin) has a slower absorption profile than the rapid-acting analogues. Older long-acting agents (e.g. NPH) have pharmacologic peaks which can lead to hypoglycaemia, especially when injected in large doses.

Recommendations for human insulins

- IM injection of NPH should be avoided since rapid absorption and serious hypoglycaemia can result [95, 96] A1.
- The thigh and buttocks are the preferred injection sites when using NPH as the basal insulin since absorption is slowest from these sites; if possible NPH should be given at bedtime rather than at dinner to reduce the risk of nocturnal hypoglycaemia [43,97] A1.
- The abdomen is the preferred site for soluble human insulin (Regular), since absorption is fastest there [16, 44, 46, 98-100] A1.
- The absorption of soluble human insulin in the elderly can be slow and these insulins should not be used when a rapid effect is needed [14,101] B2.

Recommendations for Premixed insulins

- The Regular/NPH mix should be given in the abdomen in the morning to increase the speed of absorption of the short-acting insulin in order to cover post-breakfast glycaemic excursions [12] A1.
- Any mix containing NPH should be given in the thigh or buttock in the evening as this leads to slower absorption and decreases the risk of nocturnal hypoglycaemia [93,97] A1.

3.11. Needle Length

The goal of injections with insulin, GLP-1 agents or amylin analogue is to reliably deliver the medication into the SC space, without leakage or discomfort. Choosing an appropriate needle length is crucial to accomplishing this goal. The decision as to needle length is an individual one, made conjointly by the patient and his/her HCP based on multiple factors, including physical, pharmacologic and psychological [100,102,103]. Needle lengths previously recommended for SC injection are now recognized to be too long for many adults (e.g. 12.7 mm) and for most children (e.g. 8 mm); they increase the risk of IM injections. Shorter needles are safer and are often better tolerated. Even in obese patients, studies have confirmed equal efficacy and safety/tolerability with shorter-length (5, 6 mm) needles as compared to longer ones (8, 12.7 mm) [104,105]. There is no consistent evidence to date of increases in leakage of insulin, pain, or lipohypertrophy, nor of worsened diabetes management or other complications in patient populations using shorter (4, 5, 6 mm) needles [9, 74,104-108]. Recent studies have shown that skin thickness at injection sites in a diverse population of adults with diabetes varies minimally by demographic characteristics, including BMI (e.g. obese patients have similar skin dimensions as normal-weight and thin patients) [109]. Furthermore, a 4 mm pen needle was shown to be safe and efficacious in adult patients of all sizes (i.e. equivalent glycaemic control); skin leakage was equivalent and pain scores were improved as compared with longer, wider-diameter needles [110]. In the latter study, recommended needle insertion technique was straight in (perpendicular / 90 ° angle to the skin) without a raised skin fold. A smaller study has similar results for lean children [9].

3.11.1. Children and Adolescents

Skin thickness in children is slightly less than in adults, and increases with age [111]. SC tissue patterns are virtually the same in both sexes until puberty, after which girls gain SC adipose mass, while in boys, SC tissue thickness actually declines slightly [20,112]. Hence boys may be at a higher long-term risk of IM injections [86,113,114]. The increasing prevalence of obesity in children and adolescents is an additional parameter that must now be dealt with [115].

Recommendations

- Children and adolescents should use a 4, 5 or 6 mm needle. Slim individuals and those injecting into a limb may need to lift a skin fold, especially when using a 5 or 6 mm needle [9, 83, 86,109-111,114-119] A1.
- There is no medical reason for recommending needles longer than 6 mm for children and adolescents [120] A2.
- An angled injection (at 45 °) with the 6 mm needle may be used instead of a skin fold [116] A1.
- A 4 mm needle may be inserted at 90 ° without a lifted skin fold in many children and adolescents. Some, especially thinner ones, may still need to lift a skin fold [9] A1.
- If children have only an 8 mm needle available (as is currently the case with syringe users), they should lift a skin fold and inject at 45 °. Other options are to use needle shorteners (where available) or give injections into the buttocks [113,120,121] A1.
- Avoid indenting the skin during the injection, as the needle may penetrate deeper than intended and enter the muscle B3.
- Arms should be used for injections only if a skin fold has been lifted, which requires injection by a third party A3.

3.11.2. Adults

The thickness of SC tissue in the adult patient varies widely by gender, body site and BMI [109,122-126], whereas the thickness of the skin (epidermis and dermis) is quite constant, averaging approximately 1.9-2.4 mm across injection sites, ages, races, BMI and gender; it is rarely >3.0 mm at injection sites for insulin [109,126-131]. Figure 2 summarizes observations regarding SC thickness in men and women and shows that SC fat tissue may be thin in commonly-used injection sites [47,109,122-126].

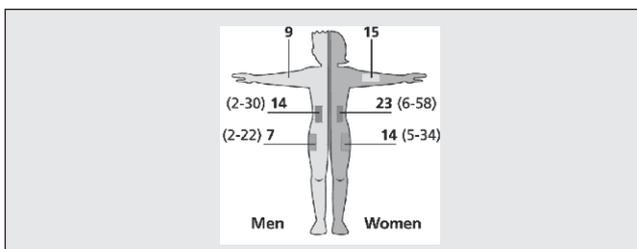


Figure 2. Subcutaneous thickness (in mm) for male and female adults. Means (in bold) and ranges (in parenthesis) reflect results from a number of ultrasound-based studies [47,109,122-126].

Recommendations

- 4, 5 and 6 mm needles may be used by any adult patient including obese ones and do not generally require the lifting of a skin fold, particularly 4 mm needles [9,74,104,106-110] A1.
- Injections with shorter needles (4, 5, 6 mm) should be given in adults at 90 degrees to the skin surface [9, 74,106-108,109,110,132] A1.
- To prevent possible IM injections when injecting into the limbs or slim abdomens, even 4 and 5 mm needles may warrant use of a skin fold. Injections with 6 mm needles should be used either with a skin fold or a 45-degree angle [9,105,106,133] A2.
- There is no medical reason for recommending needles > 8 mm. Initial therapy should begin with the shorter lengths [105,121,134] A2.
- Patients already using needles needles ≥ 8 mm should lift a skin fold or inject at 45-degrees in order to avoid IM injections [105,133] A2.

3.12. Skin Folds

Skin folds are used when the presumptive distance from skin surface to the muscle is less than the length of the needle. Lifting a skin fold in the abdomen and thigh is relatively easy (except in very obese tense abdomens), but it is more difficult to do in the buttocks (where it is rarely needed) and is virtually impossible (for patients who self-inject) to perform properly in the arm. A proper skin fold is made with the thumb and index finger (possibly with the addition of the middle finger). Lifting the skin by using the whole hand risks lifting muscle with the SC tissue and can lead to IM injections (see Figure 3) [122].

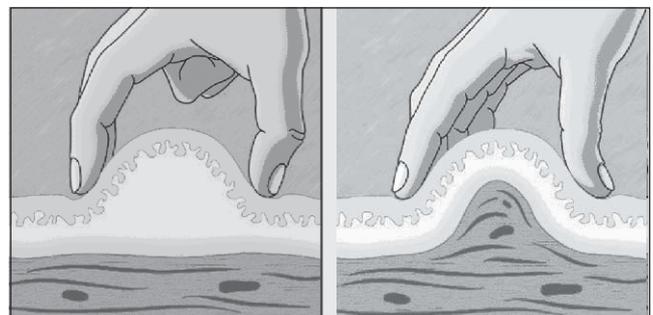


Figure 3. Correct (left) and incorrect (right) ways of performing the skin fold.

Recommendations

- Each injection site should be examined individually and a decision made as to whether lifting a skin fold is required or not given the needle length used. The recommendation should be provided to the patient in writing A3.
- All patients should be taught the correct technique for lifting a skin fold from the onset of insulin therapy A3.
- The skin fold should not be squeezed so tightly that it causes skin blanching or pain A3.

- The optimal sequence should be:
 - 1) make skin fold;
 - 2) inject insulin slowly at 90° angle to surface of skin fold (see Figure 4);
 - 3) leave the needle in the skin for 10 seconds after the plunger is fully depressed (when injecting with a pen);
 - 4) withdraw needle from the skin;
 - 5) release skin fold;
 - 6) dispose used needle safely A3.

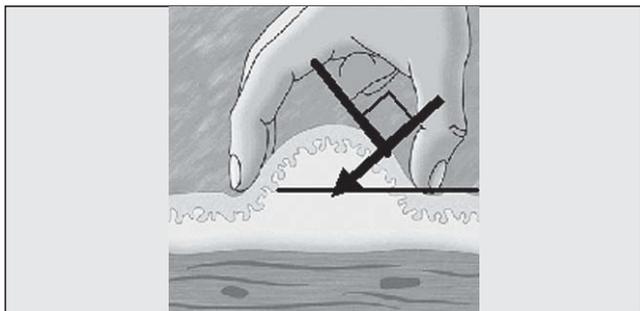


Figure 4. The correct angle of injection when lifting a skin fold (90° into the 'slope of the hill').

3.13. Lipohypertrophy

Lipohypertrophy is a thickened, 'rubbery' lesion that appears in the SC tissue of injecting sites in many patients who inject insulin. In some patients the lesions can be hard or scar-like [135,136]. Detection of lipohypertrophy requires both visualization and palpation of injecting sites, as some lesions can be more easily felt than seen [41]. Normal skin can be pinched tightly together, while lipohypertrophy cannot (see Figure 5) [137]. Both pen and syringe devices (and all needle lengths and gauges) have been associated with lipohypertrophy as well as insulin pump cannulae (when repeatedly inserted into the same location). No randomized, prospective studies have been published establishing causative factors in lipohypertrophy [54]. Published observations support an association between the presence of lipohypertrophy and the use of older, less purified insulin formulations, failure to rotate sites, using small injecting zones, repeatedly injecting into the same location and reusing needles [3,50,59,138,139].

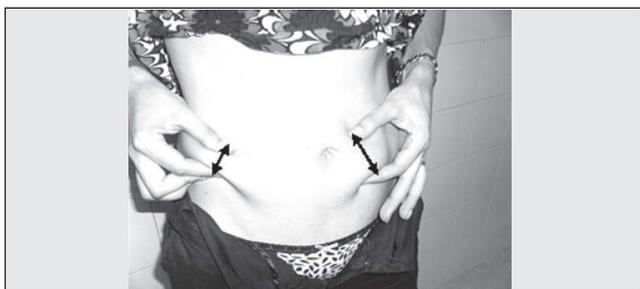


Figure 5. Palpable lipohypertrophy: normal skin (arrow tips close together) and lipohypertrophic tissue (arrow tips spread apart). (Photograph courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, Diabetes Nurses and Specialist Educators from La Paz Hospital, Madrid, Spain).

Injections into lipohypertrophic tissue may also worsen the hypertrophy. Insulin absorption may be delayed or erratic, potentially worsening diabetes management, although one study has not confirmed this [15, 50-55].

Recommendations

- Sites should be inspected by the HCP at every visit, especially if lipohypertrophy is already present. At a minimum each site should be inspected annually (preferably at each visit in pediatric patients). Patients should be taught to inspect their own sites and should be given training in how to detect lipohypertrophy [41,140] A2.
- Making two ink marks at opposite edges of the lipohypertrophy (at the junctions between normal and 'rubbery' tissue) will allow the lesion to be measured and its size recorded for long-term follow up. If visible, the lipohypertrophy should also be photographed for the same purpose A3.
- Patients should not inject into areas of lipohypertrophy until the abnormal tissue returns to normal (which can take months to years) [141,142] A2.
- Switching injections from lipohypertrophy to normal tissue often requires a decrease of the dose of insulin injected. The amount of change varies from one individual to another and should be guided by frequent blood glucose measurements [50,142] A2.
- The best current preventative and therapeutic strategies for lipohypertrophy include use of purified human insulins, rotation of injection sites with each injection, using larger injecting zones and non-reuse of needles [138-140, 143-145] A2.

3.14. Rotation of Injecting Sites

Several studies have demonstrated that the best way to safeguard normal tissue is to properly and consistently rotate injecting sites [66,146,147].

Recommendations

- Patients should be taught an easy-to-follow rotation scheme from the onset of injection therapy [148,149] A2.
- One scheme with proven effectiveness involves dividing the injection site into quadrants (or halves when using the thighs or buttocks), using one quadrant per week and moving always clockwise (see Figures 6, and 7) [150] A3.
- Injections within any quadrant or half should be spaced at least 1cm from each other in order to avoid repeat tissue trauma A3.
- HCP should verify that the rotation scheme is being followed at each visit and should provide advice where needed A3.

3.15. Bleeding and Bruising

Needles will on occasion hit a blood vessel on injection, producing local bleeding or bruising [151]. Changing the needle length or other injecting parameters does not appear

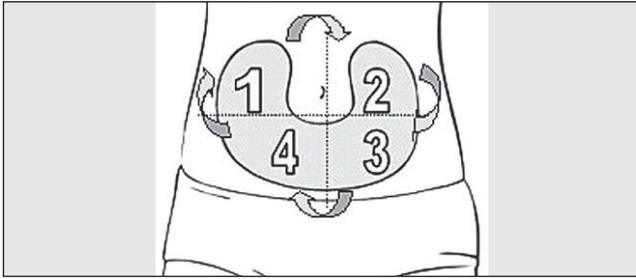


Figure 6. Abdominal rotation pattern by quadrants (Diagram courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, Diabetes Nurses and Specialist Educators from La Paz Hospital, Madrid, Spain).

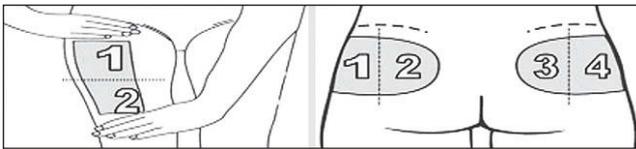


Figure 7. Thigh and buttocks rotational pattern by halves (Diagram courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, Diabetes Nurses and Specialist Educators from La Paz Hospital, Madrid, Spain).

to alter the frequency of bleeding or bruising [150] although one study [152] did suggest that these may be less frequent with the 5 mm needle.

Recommendation

Patients should be reassured that bleeding and bruising do not appear to have adverse clinical consequences for the absorption of insulin or for overall diabetes management [151,152] A2.

3.16. Pregnancy

More studies are needed to clarify optimal injecting practices in pregnancy. Use of routine fetal ultrasonography gives the HCP an opportunity to easily assess SC fat patterns and give data-based recommendations regarding injections [153]. In the absence of prospective studies it seems reasonable to make the following recommendations:

Recommendations

- Pregnant women with diabetes (of any type) who continue to inject into the abdomen should give all injections using a raised skin fold [153] B2.
- Avoid using abdominal sites around the umbilicus during the last trimester. C3.
- Injections into abdominal flanks may still be used with a raised skin fold. C3.

3.17. Safety Needles

Needlestick injuries are common among HCP with most studies showing significant under-reporting for a variety of reasons [154]. Safety needles effectively protect HCPs

against contaminated needlestick injuries [155]. Considerable education and training are needed to ensure that currently available safety needles are used properly and effectively [156].

Recommendations

- Safety needles should be recommended whenever there is a risk of a contaminated needle stick injury (e.g. in hospital) [155] B1.
- Since most safety mechanisms will not protect against needle sticks through skin folds, the use of shorter needles without a skin fold is recommended B3.
- If an IM injection is still a risk, using an angled approach (rather than a skin fold) is preferable B3.

3.18. Disposal of injecting material

Every country has its own regulations regarding the disposal of contaminated biologic waste. Options for discarding a used needle, in order of preference, are: 1) into a container especially made for used needles/syringes; 2) if not available, into another puncture-proof container such as a plastic bottle. Options for final disposal of the container, in order of preference, are to take it: 1) to a Health Care facility (e.g. hospital); 2) to another Health Care provider (e.g. laboratory, pharmacist, doctor's office). All stakeholders (patients, HCPs, pharmacists, community officials and manufacturers) bear a responsibility (both professional and financial) for ensuring proper disposal of used sharps.

Recommendations

- All HCPs and patients should be aware of local regulations. Legal and societal consequences of non-adherence should be reviewed [156] A3.
- Proper disposal should be taught to patients from the beginning of injection therapy and reinforced throughout [157] A3.
- Potential adverse events to the patients' family (e.g. needlestick injuries to children) as well as to service providers (e.g. rubbish collectors and cleaners) should be explained A3.
- Where available, a needle clipping device should be used. It can be carried in the patient kit and used many times before discarding A3.
- Under no circumstance should sharps material be disposed of into the public trash or rubbish system A3.

4. Discussion

The focus of prior injection technique recommendations [5-8] has been needle length selection, the injection process (use of skin folds and injection angle) and the choice of body

sites. This paper updates and extends the injection recommendations previously available for patients with diabetes, and covers important areas for which prior guidance was lacking: Insulin analogues (rapid- and long-acting), GLP-1 agents, pregnancy, and safety needles. Additional recommendations have been provided on topics which, though addressed earlier, still lacked detail and specificity: lipohypertrophy, pediatrics, pens, disposal of injecting material and education. These recommendations reflect our current synthesis of the available evidence, as well as expert consensus; we expect further changes following new research publications in the near future.

Regardless of patient group, the present recommendations guide the HCP and the patient towards using shorter [4, 5 or 6 mm) needles. This appears to be the most efficient means of protecting against IM injections in children and in those adults who do not lift skin folds. There is no medical rationale for the use of needles > 6 mm in children and adolescents, nor in adults (see below). This move to shorter needles is appropriate given our improved understanding of the anatomy of skin and SC adipose tissue at the common injection sites which recent studies have provided [47,109,122-131]. Recent data have been reported on precise ultrasound measurements of skin and subcutaneous tissue at insulin injection sites in a large, diverse group of adult patients with diabetes [109]. This provides important information on which to base needle-length injection recommendations, and indicates that needles as short as 4mm will consistently pass through skin and into the SC space. A separate crossover study [110] has shown that when injected straight-in (90 °) without lifting a skin fold, a 4 mm × 32G pen needle is safe and efficacious in adult patients of all sizes; that pain is less, and reports of skin leakage are numerically less than with 5 mm and 8 mm, 31G needles. An earlier, smaller study [9] suggested similar results for lean children and adults. Further studies with the new 4mm × 32G pen needle in children and adolescents will be valuable.

Although 8 and 12.7 mm needles have frequently been used in obese patients to 'ensure' SC medication delivery, recent studies have shown this is a fallacy. There is remarkable consistency of skin (dermis + epidermis) thickness in normal persons and in patients with diabetes [109,126], regardless of race, age, or BMI. Skin thickness in such studies has averaged approximately 2 mm and the maximum is rarely >3.0 mm,

indicating that needles at least 4 mm long will reliably deposit medication into the SC space. The depth of such injections (shallow versus deep SC tissue) does not appear to affect the absorption or pharmacokinetics of insulin [16]. Randomized, prospective controlled clinical trials demonstrate the lack of any change in overall glycaemic control when comparing 5 and 8 mm needles, or 6 and 12.7 mm needles, respectively, in obese patients [104,105]. Of course, if an adult patient is already using needles ≥8 mm long and there are no clinically-evident problems (e.g. unexplained glucose instability, a history of IM injections) they should continue using that needle length. We however encourage such patients to adopt a skin fold or angled injection for added safety. All patients should be apprised of the advantages of the shorter (4-6 mm) length needles, which are strongly advocated for children and adolescents. Furthermore, in adult patients *starting* on insulin there is no clinical reason for recommending a needle >6mm long, unless they are using syringes with an 8 mm needle.

Two western European countries were the first to develop and publish injecting guidelines for people with diabetes. The Danish guidelines [5] were first published in 2002, and then updated in 2006 by the Danish Nurses Organization. The Dutch guidelines [6] were published in September 2008 by the Association for Diabetes Care Professionals (EADV). Both documents are available in English. Other injecting guidelines exist, both at a local and national level (e.g. from the American Diabetes Association [7, 8]), but are not published as a separate, dedicated set like the above two.

Unlike the Dutch and Danish guidelines [5,6], the present recommendations do not require the HCP to know both the patient's BMI and the injection angle in order to choose the needle length. The BMI may not be known at the time of the visit; it may change during the course of therapy; and it can be misleading, as in patients with android obesity, very athletic build, etc. The injection angle is rarely a perfect 45 or 90 degrees and may change according to the injection site the patient uses, the use or not of a skin fold and the visual perception of the patient or observer.

A number of key injecting parameters have not been studied in sufficient depth for recommendations to be made. Table 1 presents a selective summary of these topics. Investigators are encouraged to address these issues through prospective, randomized clinical trials, where applicable.

Table 1
Key Unanswered Questions which Merit further Study

Topic	Unresolved Issues
4 mm needles	Safety, Efficacy in other populations including children/adolescents, obese adults, users of GLP-1 agonists
Lipohypertrophy	Etiology and effective prophylaxis and treatment
New insulin analogues/ GLP-1 agents	Appropriate injection sites, needle lengths and techniques to ensure optimal pharmacologic effects
Pregnant women who inject	Appropriate needle lengths and injection techniques
Needle Reuse	Prospective outcomes and risk assessment

Table 2
Top 10 New Injection Recommendations*

Needle Length	Children and adolescents should use a 4, 5 or 6 mm needle. There is no medical reason for recommending needles longer than 6 mm. The 4, 5, and 6 mm needles may be used by any adult patient, including obese ones. There is no medical reason for recommending pen needles longer than 8 mm in adults. Initial therapy should begin with shorter lengths.
Lipohypertrophy	Patients should inspect their own sites and should be given training in how to detect lipohypertrophy. They should not inject into areas of lipohypertrophy. The best current strategies to prevent and to treat lipohypertrophy include use of purified human insulins or analogues, rotation of injection sites with each injection, using larger injecting zones and non-reuse of needles.
Site Rotation	Patients should be taught an easy-to-follow rotation scheme from the onset of injection therapy.
Injection Sites	Insulin analogues and GLP-1 agents may be given at any of the injection sites as absorption rates do not appear to be site-specific. Regular insulin should be injected in the abdomen to increase rate of absorption; NPH should be injected in the thigh or buttock to slow absorption and reduce likelihood of hypoglycaemia IM injections of long-acting analogues must be avoided due to the risk of severe hypoglycaemia.
Beginning Injections in Children	Younger children may be helped by distraction techniques (as long as they do not involve trickery) or play therapy (e.g. injecting into a stuffed animal) while older children respond better to cognitive behavioral therapies.
Injections in Adolescents	Adolescents should be reassured that no one manages diabetes perfectly all the time and that occasional slip-ups, as long as they do not become habitual, are not signs of failure.
Injections in Adult Type 2 patients	The HCP should prepare all newly-diagnosed patients with type 2 diabetes for likely future insulin therapy. The HCP should explain the natural, progressive nature of the disease, stating that it includes insulin therapy and making clear that insulin treatment is not a sign of failure. Insulin therapy should be addressed positively.

* see text for references and grading scheme for the recommendations

The 'Top 10' guidance statements are summarized in Table 2. These are evidence-based and provide a concise set of recommendations for patients and HCPs which, if followed, will increase the consistent delivery of insulin and other diabetic medications into the SC space.

5. Duality of interest

All authors are members of the Scientific Advisory Board (SAB) for the Third Injection Technique Workshop in Athens (TITAN). TITAN and the Injection Technique Survey were sponsored by BD, a manufacturer of injecting devices, and SAB members received an honorarium from BD for their participation on the SAB; KS, LH and CL are employees of BD.

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Appendix

FAMILY NAME	FIRST NAME	COUNTRY
Amaya Baro	María Luisa	Spain
Annersten Gershater	Magdalena	Sweden
Bailey	Tim	USA
Barcos	Isabelle	France
Barron	Carol	Ireland
Basi	Manraj	UK
Berard	Lori	Canada
Brunnberg-Sundmark	Mia	Nordic
Burmiston	Sheila	UK
Busata-Drayton	Isabelle	UK
Caron	Rudi	Belgium
Celik	Selda	Turkey
Cetin	Lydia	Germany
Cheng, RN BSN	Winnie MW	Hong Kong
Chernikova	Natalia	Russia
Childs	Belinda	USA
Chobert-Bakouline	Marine	France
Christopoulou	Martha	Greece
Ciani	Tania	Italy
Cocoman	Angela	Ireland
Cureu	Birgit	Germany
Cypress	Marjorie	USA
Davidson	Jamie A.	USA
De Coninck	Carina	Belgium
Deml	Angelika	Germany
Diméo	Lucile	France
Disoteco	Olga Eugenia	Italy
Dones	Gianluigi	Italy
Drobinski	Evelyn	Germany
Dupuy	Olivier	France
Empacher	Gudrun	Germany
Engdal Larsen	Mona	Denmark
Engstrom	Lars	Sweden
Faber - Wildeboer	Anita	Netherlands
Finn	Eileen	USA
Frid	Anders	Sweden
Gabbay	Robert	USA
Gallego	Rosa María	Portugal
Gaspar La Fuente	Ruth	Spain
Gedikli	Hikmet	Turkey
Gibney	Michael	USA
Giely-Eloi	Corinne	France
Gil-Zorzo	Esther	Spain
Gonzalez	Amparo	USA

FAMILY NAME	FIRST NAME	COUNTRY
González Bueso	Carmen	Spain
Grieco	Gabreilla	Italy
Gu	Min-Jeong	South Korea
Guo	Xiaohui	China
Guzman	Susan	USA
Hanas	Ragnar	Sweden
Härmä-Rodriquez	Sari	Finland
Hellenkamp	Annegret	Germany
Hensbergen	Jolanda	Netherlands
Hicks	Debbie	UK
Hirsch	Laurence	USA
Hu	Renming	China
Jain	Sunil M.	India
King	Laila	UK
Kirketerp-Nielsen	Grete	Denmark
Kirkland	Fiona	UK
Kizilci	Sevgi	Turkey
Kreugel	Gillian	Netherlands
Kyne-Grzebalski	Deirdre	UK
Lamkanfi	Farida	Belgium
Langill	Ed	Canada
Laurent	Philippe	France
Le Floch	Jean-Pierre	France
Letondeur	Corinne	France
Losurdo	Francesco	Italy
Doukas	Loukas	Greece
Lozano del Hoyo	María Luisa	Spain
Marjeta	Anne	Finland
Marleix	Daniel	France
Matter	Dominique	France
Mayorov	Alexander	Russia
Millet	Thierry	France
Mkrumyan	Ashot	Russia
Navailles	M-Christine	France
Nerantzi	Afroditi	Greece
Nühlen	Ulrich	Germany
Ochotta	Isabella	Germany
Osterbrink	Brigitte	Germany
Pasaporte	Francis	Philippines
Pastori	Silvana	Italy
Penalba Martínez	María Teresa	Spain
Pizzolato	Pia	USA
Pledger	Julia	UK
Riis	Mette	Denmark

FAMILY NAME	FIRST NAME	COUNTRY
Robert	Jean-Jacques	France
Rodriguez	Jose-Juan	Spain
Roggemans	Marie-Paule	Belgium
Röhrig	Bärbel	Germany
Sachon	Claude	France
Saltiel-Berzin	Rita	USA
Sauvanet	Jean-Pierre	France
Schinz-Schweizer	Regula	Switzerland
Schmeisl	Gerhard-W.	Germany
Schulze	Gabriele	Germany
Sellar	Carol	UK
Sghaier	Rida	France
Shanchev	Andrey	Russia
Shera	A. Samad	Pakistan
Simonen	Ritva	Finland
Slover	Robert	USA
Snel	Yvonne	Netherlands
Sokolowska	Urszula	Russia
Harbuwuno	Dante Saksono	Indonesia

FAMILY NAME	FIRST NAME	COUNTRY
Starkman	Harold	USA
Strauss	Ken	Belgium
Sundaram	Annamalai	India
Svarrer Jakobsen	Marianne	Denmark
Svetic Ciscic	Rosana	Croatia
Swenson	Kris	USA
Tharby	Linda	USA
Thymelli	Ioanna	Greece
Tomioka	Miwako	Japan
Tubiana-Rufi	Nadia	France
Tuttle	Ryan	USA
Vázquez Jiménez	María del Mar	Spain
Vieillescazes	Pierre	France
Vorstermans	Mia	Netherlands
Weber	Siegfried	Germany
Webster	Amanda	UK
Wisher	Ann Maria	UK
Wulff Pedersen	Malene	Denmark
Yan Wang	Yvonne	China
Yu	Neng-Chun	Taiwan