Diabetes Ther (2023) 14:29–45
https://doi.org/10.1007/s13300-022-01332-x

REVIEW

Addendum 1: Forum for Injection Technique and Therapy Expert Recommendations, India

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Received: September 22, 2022 / Accepted: October 25, 2022 / Published online: November 15, 2022

ABSTRACT

With the emerging complexities in chronic diseases and people's lifestyles, healthcare professionals (HCPs) need to update their methods to manage and educate patients with chronic lifestyle disorders, particularly diabetes. The insulin injection technique (IIT), along with various parameters, must also be updated with newer methods. Forum for Injection Technique and Therapy Expert Recommendations (FITTER), India, has updated its recommendations to cover newer ways of detecting hypoglycaemia and lipohypertrophy, preventing needlestick injuries (NSIs), discouraging the reuse of insulin needles and encouraging good disposal. FITTER, India, is also introducing recommendations to calculate insulin bolus dose. These updated recommendations will help HCPs better manage patients with diabetes and achieve improved outcomes.

Keywords: Artificial intelligence (AI); Continuous glucose monitoring (CGM); Flash glucose monitoring (FGM); Hypoglycaemia; Hypoglycemia Awareness Questionnaire (HAQ); Insulin bolus; Insulin injection technique; Lipohypertrophy (LH); Needlestick injuries (NSIs)

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Key Summary Points

Lipohypertrophy (LH) is a common long-term complication of insulin therapy which requires early detection.

Ultrasonography is an objective and sensitive tool to detect LH. Biopsy is also a differential method to rule out LH.

Based on the level, self-monitoring of blood glucose (SMBG) hypoglycaemia should be managed by ingesting carbohydrates or intramuscular/intranasal glucagon.

Hypoglycaemia awareness training for individuals at risk of hypoglycaemia can help them prevent and better manage hypoglycaemic episodes. A tool for the detection of hypoglycaemic episodes clinically can improve hypoglycaemia awareness for healthcare professionals (HCPs).

New technologies such as continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) have been proven to be beneficial in managing hypoglycaemia in patients with type 1 (T1D) and type 2 diabetes (T2D).

Safe disposal of used sharps must be practiced in the home and hospital settings to avoid insulin needle-related needlestick injuries (NSIs).

Recent recommendation, approved by most authorities, is blood glucose goal range of 140–180 mg/dl.

To improve outcomes and minimize errors among hypoglycaemia inpatients, insulin stewardship programmes must be implemented.

Using an automated bolus calculator to improve glucose control is now accepted by patients. However, more efforts are required towards designing bolus calculators that account for individualized data.

INTRODUCTION

One of the main therapies for diabetes management in a sizeable proportion of people with diabetes is insulin injection and infusion in emergencies [1]. Insulin was discovered 100 years ago. It has impacted millions of lives worldwide, yet there is hesitation among people with diabetes and healthcare professionals (HCPs) to initiate insulin therapy in India [2]. Patients and HCPs should know about the nuances of proper insulin injections, such as injection site, site rotation, syringe reuse and their safe disposal in home and hospital settings. Because of the poor implementation of insulin injection techniques, healthcare workers (HCWs) bear a huge burden because of needlestick injuries (NSIs), which are still underreported and underestimated [3]. HCPs must also be aware of the ways to detect hypoglycaemia, as it can be asymptomatic. Diabetes management has seen progress in the way patients monitor their blood glucose levels. The newer methods of continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) have overcome many of the limitations of HbA1c and self-monitoring of blood glucose (SMBG). These methods have demonstrated improvement in diabetes management, particularly time in range (TIR), an important determinant of metabolic control related to outcomes, including hypoglycaemia [4].

To attend to the need of the hour and support the HCPs in their clinical practice, the Forum for Injection Technique and Therapy Expert Recommendations (FITTER), India, has updated the practical advice and made it more comprehensive evidence-based best practice information. The Forum will also introduce the optimal usage of artificial intelligence (AI) in insulin management for people with diabetes. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

NEWER WAYS TO DETECT LIPOHYPERTROPHY

Lipohypertrophy (LH) is a common complication of insulin therapy in the long term. One of

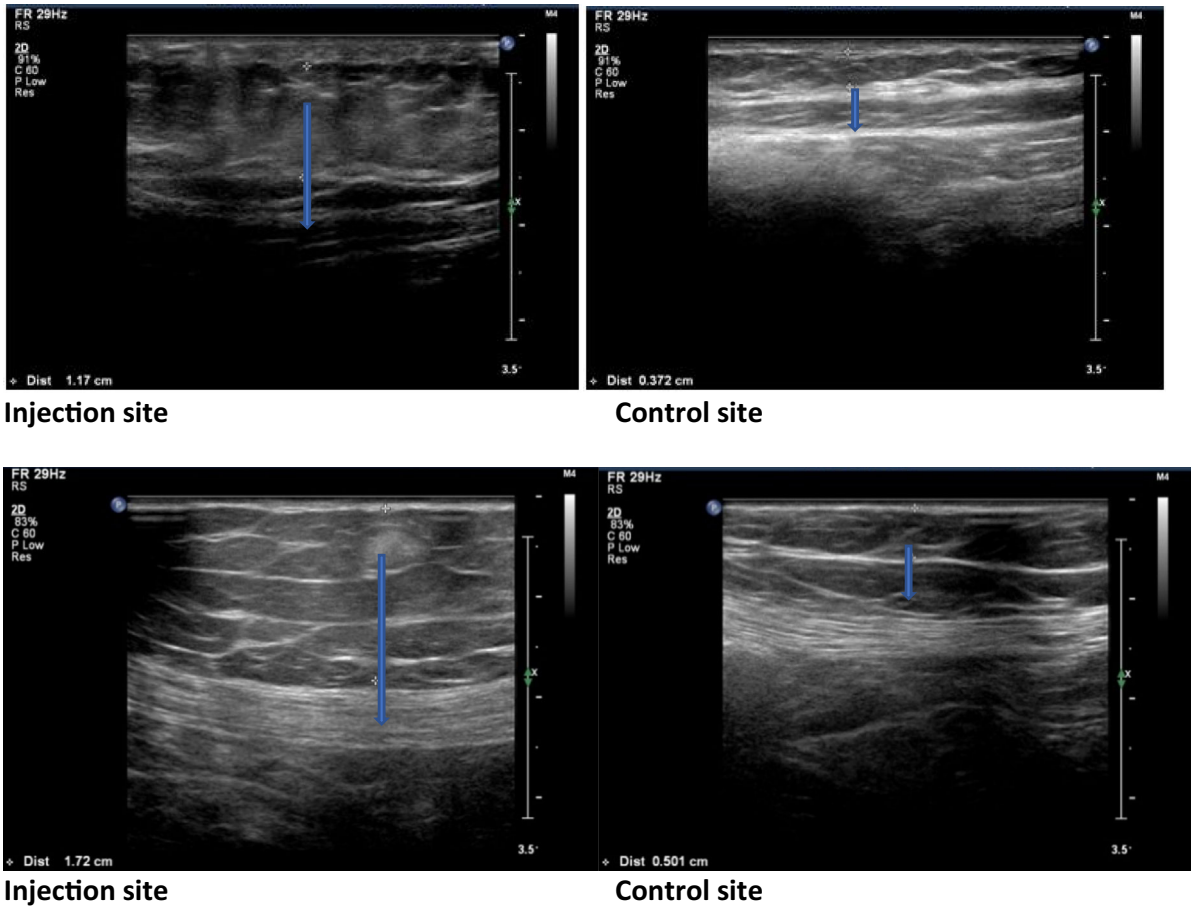

Fig. 1 Increased subcutaneous tissue thickness and heterogeneous echo texture at injection site compared to control site on ultrasonographic examination in two patients with lipohypertrophy

the largest global surveys [Injection Technique Questionnaire (ITQ) survey] of diabetes found that LH has been linked with higher rates of unexplained hypoglycaemia and glycaemic variability as well as more frequent diabetic ketoacidosis [5]. LH has been linked with incorrect rotation of injection sites, use of smaller injection zones, longer duration of insulin use and reuse of pen needles [5]. A recent Indian study has found that the prevalence of LH has a significant relationship with incorrect technique regarding injection angle, site of injection, rotation of site of injection and reuse of needles [6]. These effects are due to the erratic uptake of insulin from lipohypertrophic tissue [7, 8]. Injecting into LH can require up to 20% more than the original insulin dose (Fig. 1) [8]. The uptake is also dependent on the type of insulin used by the patients. Absorption of isophane insulin, as determined by plasma-free insulin, was found to be distinctly defective at abnormal injection sites [9], and absorption of regular insulin was delayed as determined by the clearance of I-insulin [7].

In the previous FITTER addenda, recommendations were provided to prevent and manage LH; however, there is an acute need for early and improved detection of LH for better insulin injection education [10].

Role of Imaging

Two of the key steps in insulin injection technique education are the early and accurate diagnosis of LH and educating patients to avoid injection at sites of LH [11]. However, the

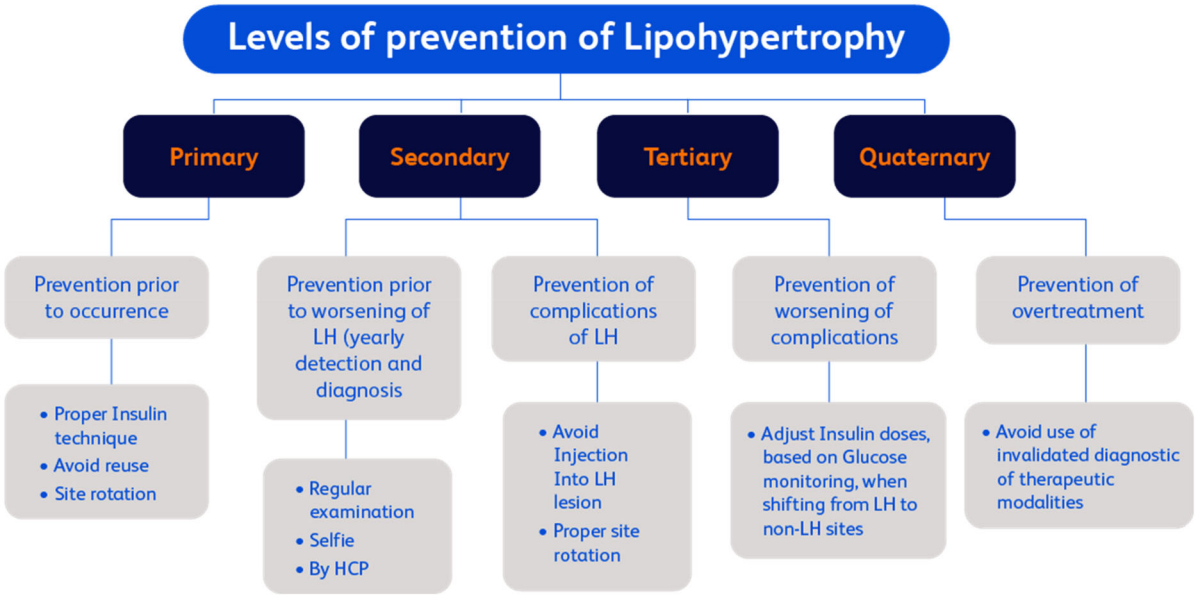

Fig. 2 Levels of prevention of lipohypertrophy. Adapted from [101]

importance of insulin injection technique and awareness of insulin-induced LH remains an overlooked challenge in diabetes care.

Ultrasonography is a novel and sensitive tool to detect LH when the clinical examination is non-contributory, as it is a more objective method [11]. In the last 5 years, several studies have reported that ultrasound could detect 40% more patients, 60% more lesions and 5 cm^2 more areas of LH lesions than physical examination [11, 12]. In addition, ultrasonography can also provide information regarding the nature and severity of LH (size, distribution and elasticity) and accurately measure the subcutaneous fat thickness, which can help HCPs to better impart insulin injection education (Fig. 2) [11].

LH can be visible, palpable but not visible or only detectable by ultrasound but not palpable or visible. Based on ultrasonographic characteristics, LH is classified as [13]:

- Simplest subcutaneous dystrophy—This is the least common form of LH, which is differentiated by a hypertrophic, nearly normal echogenic subcutaneous layer compared to the 0.5 cm in the normal subcutaneous tissue.
- Hyperechoic subcutaneous dystrophy.
  - Diffuse: This is the second most common form of LH, which is recognized by increased echogenicity spots in diffuse areas of the subcutaneous tissue where insulin is injected.
  - Nodular: This is the most common form of LH, which is seen as hyperechogenic nodules with or without small hypoechogenic areas of oedema or fluid.
  - Focal: This manifests as local asymmetric distribution of the subcutaneous fat, which may be mass-like.
  - Combination of the above.

A study showed that patients with LH or subclinical LH who were detected on ultrasonography and received insulin injection technique education based on recommended guidelines had a decrease in HbA1c and fasting blood glucose [11]. Ultrasound examination combined with insulin injection technique education significantly improved glycaemic control in patients with LH without increasing the insulin dosage. It further reduced the episodes of unexplained hypoglycaemia [11].

Role of Biopsy

A histopathological biopsy is also a reliable method to rule out LH from other injection site reactions [14]. The differential diagnosis of local site reactions in patients on insulin therapy includes LH, lipoatrophy and insulin-derived amyloidosis [15]. It is often challenging to differentiate between LH and insulin-derived amyloidosis through clinical examination and ultrasonography [14]. A study from India showed that the clinical and radiological characteristics of patients with insulin-derived amyloidosis were almost similar to those of patients with LH [16]. LH usually regresses after changing the insulin injection site with complete avoidance of injection at the lipohypertrophic site, whereas insulin-derived amyloidosis does not respond to change in the injection site. If a subcutaneous tissue mass does not regress after discontinuation of insulin injection at that site, histopathological examination for precise diagnosis should be performed [17]. There is no consensus as to when such an examination should be recommended; therefore, the clinician should approach each case individually.

Recommendations

1. Ultrasonography can be used as a tool to detect LH, especially in cases where a diagnosis cannot be established through a visual examination and palpation [11].
2. Histopathological examination is recommended to differentiate insulin-derived amyloidosis and LH [14].

DETECTION OF HYPOGLYCAEMIA

Hypoglycaemia is a key limiting factor in the glycaemic management of diabetes.

Importance of Detection and Prevention of Hypoglycaemia

Prevention of hypoglycaemia is a key feature in diabetes management. To detect hypoglycaemia, people at risk should be asked about symptomatic and asymptomatic hypoglycaemia on their visits [18]. Due to asymptomatic hypoglycaemia, patients may face hypoglycaemic unawareness. This is particularly important in patients with LH. Due to the erratic insulin absorption from lipohypertrophied tissue, patients may experience hyperglycaemia, unexplained hypoglycaemia and/or increased glucose variability. When educated about it, patients switch from injecting into lipohypertrophic to normal tissue, which may put them at risk for hypoglycaemia [8]. Intramuscular deposition often leads to faster absorption and an enhanced risk of hypoglycaemia [8]. Syringe users should ensure that their device is appropriate for the concentration of insulin they are using. A 40, 100 or 500 IU/ml syringe must be used with vials or cartridges that contain corresponding concentrations of insulin. A mismatch, e.g., using a 40 IU/ml syringe with 100 IU/ml insulin, can lead to 2.5 times higher uptake, leading to a severe hypoglycaemia. On the other hand, a 100 IU/ml syringe, along with a 40 IU/ml vial of insulin, administers only 40% of the required dose [8].

Treatment of Hypoglycaemia

Hypoglycaemia is treated through the ingestion of glucose- or carbohydrate-containing foods. HCPs should counsel individuals with diabetes to treat hypoglycaemia with fast-acting carbohydrates at the hypoglycaemia alert value of $\leq$ 70 mg/dl (3.9 mmol/l) [18]; 15–20 g glucose is the preferred treatment for the conscious individual with blood glucose $<$ 70 mg/dl (3.9 mmol/l) [18]. Even if SMBG shows hypoglycaemia 15 min after the treatment, the same treatment should be repeated [18]. When the blood glucose returns to normal, the individual should consume a meal or snack rich in complex carbohydrates, like cereal, to avoid hypoglycaemic relapse [18]. One must repeat snacks at 3-h intervals till the effect of the offending drug wanes.

Glucagon is the choice of treatment for blood glucose $<$ 54 mg/dl (3.0 mmol/l). If the individual is unable to consume carbohydrates by mouth, the use of glucagon is indicated for

the treatment of hypoglycaemia [18]. Caregivers, school staff and family members should be able to access and be aware of when and how to administer it [18].

For severe hypoglycaemic episodes, injectable glucagon has been the standard of care [19]. Commonly, injectable glucagon comes in a vial with 1 mg lyophilised human synthetic glucagon and a syringe pre-filled with 1 ml sterile saline, which is to be reconstituted prior to usage. More recently, ready-to-use glucagon in pre-filled syringes has become more available [20]. In December 2020, a generic version was also approved [21].

Glucagon also comes in an intranasal ready-to-use 3 mg dosing spray bottle [22]. The bottle's tip is inserted into the nostril and sprayed. The powdered glucagon is designed to be absorbed in the mucosal lining of the nasal cavity without having to reach the respiratory or olfactory mucosa. So, intranasal glucagon works even if the person is not conscious or is experiencing nasal congestion. Evidence suggests that nasal glucagon can be delivered in well under a minute by untrained individuals [23] and is effective within 5 min of administration but does not sustain the effect as seen with injectable glucagon. As the nasal glucagon has a shorter duration of action than intramuscular glucagon [22–24].

Hypoglycaemia Unawareness and Hypoglycaemia Awareness Education

Impaired awareness of hypoglycaemia is a major predictor of its severity [22, 25]. Individuals at risk of hypoglycaemia should be equipped to anticipate and suspect hypoglycaemic episodes so that preventive and immediate corrective measures can be taken. This can be achieved through hypoglycaemia awareness training [26].

A detailed tool for the detection of hypoglycaemic episodes clinically and improvement in hypoglycaemia awareness, called the Hypoglycemia Awareness Questionnaire (HAQ), is available. It is a simple, structured tool with 12 questions, as shown in Table 1. Of these, four relate to adrenergic symptoms, four to neuroglycopenia and two to nocturnal hypoglycaemia. This questionnaire elevates the history-taking skill of the diabetes care professional and offers a checklist for screening an important acute complication of diabetes [27].

Table 1 Hypoglycemia Awareness Questionnaire (HAQ) [27]

	Never	Once	More than once
In the past one week, have you experienced unusual episodes of:			
Feeling of uneasiness	0	1	2
Profuse sweating, not explained by ambient temperature	0	1	2
Trembling/shaking	0	1	2
Palpitations	0	1	2
Uncontrollable hunger	0	1	2
Difficulty in thinking, concentrating, speaking, seeing, hearing or moving	0	1	2
Altered movements or seizures	0	1	2
Extreme weakness/giddiness/dizziness	0	1	2
Loss of consciousness or fainting	0	1	2
Disturbed sleep/nightmares	0	1	2
Early morning headaches	0	1	2
Documented, reliable low blood glucose values	0	1	2

Importance of Newer Glucose Monitoring Systems

Increased frequency of glucose monitoring relates to lower hypoglycaemia risk and improves TIR, which is associated with

improved A1C [28]. The conventional method for assessment of glucose control is denoted by HbA1c and SMBG. These approaches are effective but have several limitations. HbA1c does not pick up intra- or inter-day variability [29], does not reflect postprandial values [29] and is an unreliable measure in patients with anaemia [29, 33], haemoglobinopathies [30, 33] or iron deficiency [31, 33], pregnancy [32, 33] and severe kidney disease [33], which are linked with a higher risk of acute events or micro- and macrovascular complications [29].

New diabetes technologies have been shown to overcome these limitations. SMBG and, for some patients, CGM are essential tools to assess therapy and detect incipient hypoglycaemia. These include real-time continuous glucose monitoring (RT-CGM) and FGM, also known as intermittently scanned CGM.

FGM, like Libre, is a pre-calibrated sensor-based technology characterized by a small-sized patch lasting up to 14 days and a short warm-up period. The IMPACT study evaluated FGM in people with type 1 diabetes (T1D) and found a 38% reduction in time in hypoglycaemia after the use of FGM technology for 6 months [34]. The REPLACE study evaluated FGM in people with type 2 diabetes (T2D) and found that time in hypoglycaemia < 70 mg/dl was reduced by 43% and 55 mg/dl by 53% after the use of FGM technology for 6 months [35].

RT-CGM has added functionality of alarms for low and high glucose levels and may be integrated with insulin pumps. There is strong evidence for its utility in patients with either T1D or T2D and with either personal or professional CGM systems [36]. In people with T1D and T2D with A1C above target, CGM improved A1C between 0.3 and 0.6% [18]. Patient benefits include improvement in A1C, reductions in hypoglycaemia and glycaemic variability, and greater treatment satisfaction and an improved sense of mental well-being [37–40]. CGM data also give HCPs insight into patients' behaviours and glycaemic patterns and may reveal previously missed hypoglycaemia [41, 42]. CGM data help in modulating therapy and can provide an opportunity for education. CGM also has applications in the management of patients with frequent severe hypoglycaemia, often associated with hypoglycaemia unawareness [28]. The Diabetes Tele Management System (DTMS) is a telemedicine-based follow-up programme designed to provide individualized therapy advice on glycosylated haemoglobin, blood pressure and low-density lipoprotein customized to multiple patient characteristics, which helps attain the goals of therapy [43].

Recommendations

1. Conscious individual: 15–20 g oral glucose is the preferred treatment for the conscious individual with blood glucose < 70 mg/dl [18] or IV glucose if blood glucose is < 50–25% dextrose IV 50 or 100 ml.
2. Injection glucagon is the choice of treatment for blood glucose < 54 mg/dl for people incapable of or reluctant to consume carbohydrates by mouth [18].

PREVENTION OF NSI, REUSE OF INSULIN NEEDLES AND GOOD DISPOSAL

NSIs with insulin needles or lancing devices are among the highest frequency needle injuries in the healthcare setting [44]. Pen injection devices aspirate human cells back into the cartridge [45]. When an NSI occurs, these potentially infectious cells can be deposited back into the needle and then transmitted accidentally through both ends [46].

Needle reuse causes the blunting and bending of the needle tip, increasing the risk of bleeding, bruising or scarring, dosage inaccuracy and LH [10]. The reuse of insulin syringes, pens and needles by patients, as well as the HCPs, potentially exposes them to NSI and increases the risk of blood-borne pathogen transmission [8]. This addendum will discuss NSI and reuse in home and hospital settings, along with good disposal practices.

NSI and Reuse at Home and Hospital Settings

A worldwide ITQ survey revealed that 40% of participants reused needles (pen/syringe) 3–5 times and a significantly higher LH was associated with incorrect rotation of sites and with needle reuse [5]. The Indian results of the ITQ survey revealed that 80% of participants reused needles more than three times [47]. Most used diabetic sharps ended up in public trash and constituted a high risk for NSI. Pain was associated with larger needle size and needle reuse and increased as a function of the number of times the needle was reused [5]. According to the Centers for Disease Control and Prevention (CDC) report, an estimated 385,000 sharp injuries take place every year among the HCWs in hospitals globally [48]. HCWs do not report > 50% of the NSIs, so the actual NSI incidence is estimated to be much higher and should not be underestimated [49].

A cross-sectional study revealed that 79% of patients did not receive any guidance about the single use of needles and syringes from HCPs [50]. In India, patients frequently reuse syringes and pen needles for various reasons, including cost [47]. Pen needles and insulin syringes are ideally single-use products and should never be reused [47].

NSIs create a burden for caregivers and HCPs in terms of anxiety, stress and morbidity [51]. In India, 23.5% of all injections were reused [52], only 22.5% of injections were administered with a sterile syringe and needle [53], and the rate of NSIs is estimated as 0.051 per 1000 injections administered [54]. The reuse of a syringe from an infected to a healthy patient as well as an NSI to an HCP after using the needle on an infected patient can cause blood-borne infection transmission. The cost of managing blood-borne infections poses a substantial financial burden for the healthcare system. Much of this financial burden is borne by households in India through out-of-pocket expenditures [55, 56].

Good Disposal

The percentage of diabetes patients practicing improper sharp disposal practices is as high as 86–97% [57, 58]. Worldwide ITQ 2014–2015 survey found that > 40% of used diabetes sharps still wind up in the community trash. Only 20.7% of patients use a container specially made for used sharps [59]. The ITQ 2014–2015 (Indian arm) found that nearly 65% of patients never received any training on proper sharp disposal [60].

Recommendations

1. Avoid recapping, bending or breaking needles. Disposal of needles in the household or public disposal system should also be avoided. Use a needle snipping device and puncture-resistant container.
2. Patients must be educated on the safe disposal of their used sharps with reminders during the follow-up visits. They must also be educated to follow the local regulations regarding sharp disposal, avoiding their disposal in the public garbage bins or household trash.
3. HCPs should identify the high-risk groups with insulin delivery difficulties, such as people with LH, obese people, the elderly and those with visual problems [61].

INSULIN USE IN CRITICAL CARE SETTINGS

Insulin Use in Critical Care Settings, Intravenous and Intramuscular Insulin Injections

HCPs, including intensivists and endocrinologists, face a unique challenge in glycaemic control in the critically ill as these patients invariably have multiorgan dysfunction [62]. Insulin resistance may lead to hyperglycaemia in critically ill patients, even those who have not previously had diabetes [63]. In addition,

hypoglycaemia enhances morbidity/mortality in critically ill diabetic patients [64].

The previous FITTER addenda suggested recommendations for insulin use in critical care settings. However, there is a need for updated recommendations based on newer evidence. Evidence suggests a tighter control in the range of 110–140 mg/dl in surgical patients, but a less aggressive target may benefit medically ill patients [65] as such rigorous targets can cause severe hypoglycaemia (< 40 mg/dl). Recent recommendation for the goal range, which is approved by most authorities, is 140–180 mg/dl [66]. When blood glucose levels are > 180 mg/dl, the only acceptable therapy is the initiation of continuous IV insulin infusion [67].

- For patients with medical morbidity, blood glucose level at a range of 140–180 mg/dl should be maintained [62].
- For patients with surgical morbidity, blood glucose level at a range of 110–140 mg/dl should be maintained [62].
- Only IV insulin should be given [62].
- Avoid subcutaneous therapies with premixed insulin, intermediate- or long-acting insulin and SSI [62].
- Regular insulin or rapid-acting insulin analogues can be used as an IV infusion [62].
- An overlapping period of 1–2 h should be given prior to changing from IV to subcutaneous insulin. The overlap can be lowered to 15–30 min if rapid analogues are used [62].

Certain factors which are considered vital for an insulin infusion system include the usage of a validated insulin titration programme, access to suitable staffing resources, accurate monitoring technology and standardized infusion preparation methods, delivery of consistent carbohydrate calories and nutritional provision, and dextrose replacement for hypoglycaemia prevention and treatment [67].

Intramuscular injections should be avoided, especially with long-acting insulins, as they end up working like rapid-acting insulin and may result in severe hypoglycaemia [8]. In an evidence case report, a 24-year-old female with T1D experienced severe hypoglycaemia repeatedly when she switched to insulin glargine from NPH insulin at equal daily doses. It was found that she often injected herself in muscle tissue, which led to unexpected rapid insulin action. When the injection technique was corrected, hypoglycaemia did not recur. The long-acting kinetics of insulin glargine need precipitation in the subcutaneous tissue. Therefore, it is vital to review each patient's injection technique when treatment with long-acting insulin is started [68]. The absorption rate is also dependent upon the subcutaneous and intramuscular sites. The intramuscular absorption rate is faster but is not recommended for routine use. It can be given under certain circumstances, such as diabetic ketoacidosis, dehydration, etc. [69]. Regular insulin or rapid-acting insulin analogues can be injected intramuscularly to achieve rapid control of hyperglycaemia and may avert the need for patients to be admitted to hospitals with diabetes and ketosis [70]. Intramuscular insulin infusion has also been reported as a modality of treatment for brittle diabetes [71].

Insulin Stewardship for Inpatient Hyperglycaemia

Intravenous insulin use can be linked with several potential errors which may have unintentional adverse effects. Hypoglycaemia is a concerning common side effect of insulin followed by weight gain presenting as oedema and diabetic ketoacidosis. Subcutaneous insulin injection may also result in LH, lipoatrophy and infection. Incidences of local and systemic hypersensitivity and anaphylaxis have markedly decreased with the use of purer forms of insulin. Thorough knowledge of various aspects related to insulin injection techniques such as intravenous insulin preparation, correct dosage calculation, precautions while using insulin with various intravenous fluids, formulating strategies to minimize insulin adsorption to tubing surface and choosing appropriate insulin injection accessories and devices can help in optimal control of hyperglycaemia with minimal errors [72]. Moreover, intensive settings also lead to a high load of hyperglycaemia [73]. This adds to the complexity of in-hospital management and creates challenges for both patients and HCPs.

These obstacles to patients and HCPs' health must be addressed through a comprehensive insulin stewardship programme, which will tackle all aspects of safe and rational insulin use. Such a policy should strategize standard operating procedures which manage the choice of insulin regimes, preparations and delivery devices. This will reduce the chances of inappropriate prescription and administration. There are various aspects that can be included in the stewardship programme (Table 2).

To evaluate the performance of the stewardship programme, audits must be conducted periodically. The following metrics can be used to quantify the success of the programme:

- Reduction in medication errors—wrong dose or type of medication given.
- Reduction in insulin administration errors—inaccurate time, incorrect technique.
- Reduction in hypoglycaemia rates.
- Percentage of correct management of hypoglycaemia.
- Percentage of patients completing insulin education.
- Correct disposal of needles and syringes [74, 75].

Table 2 Aspects of insulin stewardship

Insulin inventory
Preparation/trade name
Strength
Delivery device
Insulin initiation
Prescription
Counselling
Technique
Insulin monitoring
Glucose monitoring
Hypoglycaemia awareness training
Titration regimen
Insulin safety
Technique for nursing/medical staff
Disposal
Troubleshooting for needlestick injuries

The rewards of an insulin stewardship programme are manifold and must be vigorously pursued to improve patient outcomes and minimize errors.

ARTIFICIAL INTELLIGENCE IN INSULIN/AUTOMATION OF INSULIN BOLUS DOSE CALCULATION IN T1D

In the past few years, the use of machine learning models has increased for the prediction of hypoglycaemia. The timely prediction of a hypoglycaemic episode can not only improve the quality of life of T1D patients but also save their lives [76]. Even though insulin pumps and CGM technologies have been adopted [76], fewer than one-third of people with T1D achieve their diabetes management goals [77]. The Diabetes Control and Complications Trial (DCCT) reported that regular and frequent insulin dose adjustments might improve glycaemic control among people with T1D or T2D [78]. If subcutaneous insulin is prescribed, a basal bolus regimen is the therapy of choice for all people with type 1 diabetes. The first step in the optimization of insulin therapy is defining the right basal insulin dose. A stable dose of bolus insulin would ensure constant blood glucose levels in between meals. Bolus dose estimation needs more work and effort. As a bolus dose would vary as per food taken, prescription of a constant dose of bolus insulin generally does not result in an optimal outcome. Carbohydrate counting and estimating the insulin-carbohydrate ratio are the scientific ways to estimate the bolus insulin dose [79]. Many mobile applications are available for calculating carbohydrates in a given food item. Certain algorithms are used to detect the composition of food based on images, thereby helping in carbohydrate counting [80]. In this addendum, we will introduce the concept of

using artificial intelligence (AI) in insulin management for people with diabetes.

Automated Bolus Calculation

Diabetes healthcare has seen increasing development of AI-based tools over the last few years [81]. The use of insulin meal bolus calculators has improved post-prandial glucose control, reduced dosing errors, alleviated fears of hypoglycaemia and elevated confidence in self-management among individuals with diabetes [82–86].

Insulin bolus counting is a complex process which requires an understanding of pre-prandial glucose level, amount of carbohydrate intake, insulin sensitivity, insulin-to-carbohydrate ratio and active insulin on board. Due to the time-consuming nature of manual bolus calculations, people are usually unwilling to perform this task [87] and often choose empirical estimates when determining insulin doses [88]. This can result in errors and cause severe clinical consequences. Automated bolus advisors quantify bolus insulin dosages automatically to include carbohydrate grams and address abnormal blood glucose levels based on the estimation of individualized insulin parameters. Several models of bolus calculators are available on the market, which predict the basal insulin dose using algorithms and AI techniques [89–97]. Such devices help ease the burden of diabetes self-management, decrease the therapy burden, offer improved accuracy of insulin boluses and lower the risk of long-term complications [90].

Some of the currently available glucometers/insulin pumps claim to predict bolus dose; however, people need to count carbohydrates and determine insulin-carbohydrate ratios on their own. These systems only automate the mathematical calculation part of bolus dose prediction. An ideal integrated system should be able to calculate food carbohydrates and help determine insulin carbohydrate ratio.

Clinical Aspects of the Bolus Calculator

Programming the bolus calculator in accordance with the principles of intensive functional insulin therapy requires extensive experience as a physician and good cooperation with the patient. Proper blood glucose self-monitoring using a blood glucose meter or CGM is essential [98]. The use of an automated bolus calculator is now widely accepted by patients and has been shown to improve glucose control [89] and reduce glycaemic variability [99].

Recommendations

Typically, when setting the bolus calculator, the following parameters must be determined individually for each patient [99]:

1. Insulin-to-carbohydrate ratio (ICR): For the initial determination of ICR, the rule of 500 should be used; 500 is divided by the total daily insulin dose (DDI) to get the grams covered by 1 unit of insulin [99]; 500/50 = 10 g. The normal recommendation is to give 1 unit of insulin for every 15 g. However, this formula is just the starting point and ICR needs to be tweaked further for each individual.
2. Insulin sensitivity (correction factor): 1800 rule is used in which 1800 is divided by the DDI to get the average blood glucose reduction after administration of 1 unit of insulin [99]. Like ICR, this formula only provides a standard starting reference and needs to be personalized.
3. Target blood glucose: Target blood glucose values should be decided as per the clinical scenario. At the same time, the ideal bolus dose calculator should have the flexibility to allow mid-course correction in case of a change in the clinical situation. Relatively, higher values of glucose are targeted at night compared to the daytime because hypoglycaemia awareness may be compromised. Usually, these values range between 80 and 120 mg/dl [99].
4. Active insulin time (insulin on board): Active insulin time ascertains how long the bolus calculator algorithm will include

bolus insulin and is based on the personal insulin pump providing information on the quantity of the active insulin that is already in the body. Insulin on board varies according to the type of insulin used and the dose taken. There are standard formulae that can be used to calculate active insulin time (AIT). It is vital to include this calculation in bolus dose calculators to avoid overdosing and stacking. In adults, this parameter is programmed for 3–4 h. It depends on the bolus size, and for boluses > 10–15 units, the programmed time can be prolonged to 5 h [99].

Factors affecting insulin bolus dose might also include intensity, timing and duration of exercise; glycaemic index, insulin load and glycaemic load of food; and concurrent intake of alcohol. Contemporary bolus calculators do not consider these factors, but efforts towards improvement are ongoing [100].

CONCLUSION

These FITTER, India recommendations intend to raise awareness on crucial issues among healthcare professionals and patients and improve insulin practices. This new, evidence-based, practical and comprehensive set of recommendations provides the tools, approaches and practices that will help the health system adopt advanced and correct injection techniques and safe use of anti-diabetic injectable therapies.

ACKNOWLEDGEMENTS

Funding. The Rapid Service Fee was funded by emediscene.

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

Author Contributions. Dr Sanjay Kalra contributed to the study conception and design. All the authors read, reviewed and approved the final manuscript.

Disclosures. Sanjay Kalra (corresponding author), Unnikrishnan Ambika Gopalakrishnan, Kanakatte Mylaraiah Prasanna Kumar, Rakesh Sahay, Hemraj Balchand Chandalia, Banshi Saboo, Sundaram Annamalai, Jothydev Kesavadev, Rishi Shukla, Subhash Kumar Wangnoo, Manash Pratim Baruah, Jubbin Jacob, Ganapathi Bantwal, Saurabh Arora, Rajiv Singla, Suresh Kumar Sharma and Suresh Damodaran have nothing to disclose in relation to the present study.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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