




ORIGINAL RESEARCH

Indian Injection Technique Study: Injecting Complications, Education, and the Health Care Professional

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ABSTRACT

Introduction: Using the Indian and rest of world (ROW) injection technique questionnaire (ITQ) data, we address key insulin injection complications.

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Methods: In 2015 we conducted an ITQ survey throughout India involving 1011 patients. Indian values were compared with those from 41 other countries participating in the ITQ, known here as ROW.

Results: More than a quarter of Indian insulin users described lesions consistent with lipohypertrophy (LH) at their injection sites and approximately 1 in 5 were found to have LH by the examining nurse (using visual inspection and palpation). Just over half of Indian injectors report having pain on injection. Of these, 4 out

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of 5 report having painful injections only several times a month or year (i.e., not with every injection). Doctors and diabetes educators in India (as opposed to nurses) have a larger role in teaching patients how to inject than they do in ROW. Despite this specialized approach, a very high percentage of patients report that they have not been trained (at least cannot remember being trained) in a wide range of essential injection topics. Only about 30% of Indian injectors get their sites checked at least annually, with nearly a third only having sites checked when they specifically complained and nearly 4 out of 10 never having had their sites checked.

Conclusion: Indian HCPs can clearly do a better job covering all the vital topics essential to proper injection habits.

Keywords: Infusions; Injections; Insulin; Lipodystrophy; Lipohypertrophy; Needles; Needlestick; Subcutaneous

INTRODUCTION

In a previous paper we introduced the Indian injection technique questionnaire (ITQ) survey patient population and injecting practice [1]. In conjunction with the results, we gave evidence-based Indian best practice recommendations. Here we use the same approach for injecting complications.

METHODS

Our previous paper [1] described the methods, materials, centers, and patients who participated in the study.

All procedures followed were in accordance with the ethical standards of the Indian Council of Medical Research, the responsible committee on human experimentation (institutional and national), and the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Lipohypertrophy (LH)

Patients were asked: “Do you have any swelling or lumps under the skin at your usual injection sites that have been there for some time (weeks, months, or years)?” Table 1 gives the results for both the patients’ answers and the nurses’ examination of all patient injecting sites. Indian results are given beside rest of world (ROW). The latter constitute the values from the 41 other ITQ participating countries combined (excluding India).

Nurses examined each of the patient’s injection sites both visually and by palpation and reported any LH (Table 2). Percentages for both visual and palpated LH in India were

Table 1 Lipohypertrophy in India vs ROW

| Presence of lipohypertrophy | % India (N = 873) | % ROW (N = 7657) |
|-----------------------------|----------------------|---------------------|
| As per patient report | 25.9 | 29.2 |
| As per nurse examination | 21.9 | 31.8 |

ROW (rest of world) constitutes the values from the 41 other ITQ participating countries combined (excluding India)

Table 2 Nurse-reported lipohypertrophy in Indian and ROW patients

| Site | Exam type | % India (N = 837) | % ROW (N = 7565) |
|----------|-----------|----------------------|---------------------|
| Abdomen | Visual | 6.8 | 17.3 |
| | Palpation | 9.3 | 21.1 |
| Thigh | Visual | 6.9 | 9.8 |
| | Palpation | 8.7 | 11.2 |
| Buttocks | Visual | 3.4 | 2.1 |
| | Palpation | 0.0 | 2.8 |
| Arm | Visual | 9.4 | 11.2 |
| | Palpation | 10.1 | 13.4 |

slightly lower than in ROW. When nurses found LH they were asked to measure the lesions along their longest dimension in millimeters. Table 3 shows that LH size in Indian patients was on average slightly lower in the abdomen and thigh and slightly higher in the arm. Whenever nurses found LH they asked the patient if they were still injecting into it and 18.9% of Indian patients said yes. They were then asked how often they did so (Table 4). Patients who injected into LH were also asked why they did so (Table 5). More than half of Indian patients answered ‘Don’t know’ to that question.

The worldwide ITQ data [2, 3] showed a strong association between the presence of LH and the total daily dose (TDD) of insulin. Over 10 IU of insulin on average was consumed in the LH+ population vs LH-. In T2DM patients, this average TDD difference is 13.5 IU. In T1DM patients, the average TDD difference is 5.4 IU. The presence of LH is associated with higher HbA1c values, an average difference of 0.55. The worldwide data also showed that LH is associated with incorrect rotation of injection sites, using smaller injecting zones, more years on insulin, and reusing pen needles. The higher the number of times the needle is reused, the more frequently reported LH is.

Table 3 Size of nurse-measured lipohypertrophy for Indian and ROW patients

| Size of lipohypertrophy (mm) | Mean India | Mean ROW | N India | N ROW |
|------------------------------|------------|----------|---------|-------|
| Abdominal | 39.1 | 44.7 | 62 | 1258 |
| Thigh | 40.4 | 42.0 | 27 | 460 |
| Arm | 39.0 | 35.5 | 21 | 372 |

Table 4 Frequency of injection into lipohypertrophy in Indian and ROW patients

| Frequency | % India (N = 118) | % ROW (N = 1964) |
|-----------------------|-------------------|------------------|
| Every injection | 6.8 | 16.7 |
| Frequently (daily) | 28.8 | 39.5 |
| Occasionally (weekly) | 44.1 | 30.3 |
| Seldom (monthly) | 20.3 | 13.5 |

We defined “hypoglycemia” as the occurrence of at least one symptom of low sugar (e.g., palpitations, tiredness, sweating, strong hunger, dizziness, tremor) and a confirmed blood glucose meter reading of no greater than 60 mg/dL (3.3 mM/L). We defined “frequent unexplained hypoglycemia” as hypoglycemia occurring one or more times weekly in the absence of a definable precipitating event such as a change in medication, diet, or activity. We defined “glycemic variability” as the presence of blood glucose oscillations from less than 60 mg/dL (3.3 mM/L) to more than 250 mg/dL (13.9 mM/L) at least three times a week in an unpredictable and unexplained fashion and evidence of such a pattern for at least the previous 6 months.

Nurses were asked to review the records of each subject in the ITQ and assess how many qualified as having “frequent unexplained hypoglycemia” and “glucose variability”. Approximately 1 out of 4 Indian insulin injectors had frequent unexpected hypoglycemia and more than 1 out of 3 had glucose variability (Table 6). These findings are proportionally

Table 5 Reasons patients report injecting into lipohypertrophy in Indian and ROW patients

| Reason | % India (N = 158) | % ROW (N = 2160) |
|--------------------|-------------------|------------------|
| It is convenient | 4.2 | 16.3 |
| It is less painful | 13.3 | 22.3 |
| Just a habit | 29.7 | 34.9 |
| Do not know | 52.8 | 26.5 |

Table 6 Frequency of unexpected hypoglycemia and glucose variability in Indian patients

| | % India | % ROW | N India | N ROW |
|-------------------------|---------|-------|---------|-------|
| Unexpected hypoglycemia | | | | |
| Yes | 24.1 | 19.4 | 236 | 1580 |
| No | 75.9 | 80.6 | 745 | 6558 |
| Glucose variability | | | | |
| Yes | 37.3 | 35.4 | 369 | 2872 |
| No | 62.7 | 64.6 | 621 | 5251 |

Table 7 Nurse-reported lipoatrophy and redness in Indian and ROW patients

| Site | Finding | % India (N = 837) | % ROW (N = 7565) |
|----------|-------------|----------------------|---------------------|
| Abdomen | Lipoatrophy | 0.4 | 0.6 |
| | Redness | 5.7 | 3.3 |
| Thigh | Lipoatrophy | 1.2 | 0.5 |
| | Redness | 5.4 | 2.8 |
| Buttocks | Lipoatrophy | 0.0 | 0.2 |
| | Redness | 3.4 | 0.4 |
| Arm | Lipoatrophy | 0.7 | 0.4 |
| | Redness | 2.4 | 3.6 |

similar in India to ROW. In general, LH is associated with higher rates of unexplained hypoglycemia and higher rates of glycemic variability as well as more frequent diabetic ketoacidosis (DKA). Nurses also assessed injection sites for lipoatrophy and redness, and Table 7 gives the results for India and ROW.

Rotation of Injecting Sites

Correct site rotation is defined as always injecting at least 1 cm from a previous injection. Worldwide ITQ data shows that patients who rotate correctly tend to have less hyperglycemia, less LH, less unexplained hyperglycemia, and less glucose variability. (Data not shown for the aforementioned, but all differences were significant to a $p < 0.05$.) HbA1c is lower in those who correctly rotate by an average of 0.53. Correct rotation is also associated with lower TDD by an average of 4.7 IU. Table 8 shows that 68.1% of Indian injectors were found to correctly rotate site, a value similar to that in ROW.

Table 8 Lipohypertrophy and correct rotation: India vs ROW

| | India (N = 873) | ROW (N = 7657) |
|---------------------------|--------------------|-------------------|
| Practice correct rotation | 68.1 | 71.0 |

Bleeding, Bruising, Pain, and Leakage

Indian patients were asked if they ever observed bleeding or bruising from their injection sites and 41.4% said they did. They were then asked about the frequency and only 0.9% said it was “always”, 7.8% said “often” (several times a week), 53.6% said “sometimes” (several times a month), and 37.7% said it was “almost never” (several times a year).

We found that just over half of Indian injectors report having pain on injection. Of these, 4 out of 5 report having painful injections only several times a month or year (i.e., not with every injection). Pain seems also to be commonly associated with bleeding. Approximately 1 out of 5 Indian patients report leakage of insulin from the skin. Of these, approximately 85% say it occurs rarely (several times a month or a year).

Indian patients were asked who gave them their injection training. Table 9 makes clear that doctors and diabetes educators in India have a larger role in teaching patients how to inject than they do in ROW. Pharmacists and industry representatives are also more engaged in India than ROW. Health care in India is often delivered in very rapid physician visits and diabetes care is no exception; it is common for a physician to see from 50 to 100 outpatients in a day. Injection training is still considered the *prevue* of the doctor in India.

Table 9 Professional who gave patient injection training

| Injection instructor | % India (N = 986) | % ROW (N = 9440) |
|--|----------------------|---------------------|
| General nurse | 13.9 | 22.9 |
| Diabetes nurse | 15.7 | 46.7 |
| Diabetes educator | 23.4 | 12.3 |
| Doctor (general practitioner) | 15.3 | 5.1 |
| Doctor (diabetes specialist) | 17.1 | 10.0 |
| Pharmacist | 7.8 | 2.0 |
| A representative of the pen or needle manufacturer | 6.7 | 1.0 |

Indian patients were asked how often their injection sites were checked by their HCP. Table 10 shows that in India, as in ROW, the goal of checking injection sites at least once a year is not being met for the majority of patients. Patients were asked when they last received instruction or advice on injections. Table 11 shows that India is actually performing slightly better than ROW in giving advice within the last year.

Indian patients were asked to report which injection topics they *could not remember ever being trained in*. Table 12 shows that for all topics, a higher percentage of Indian patients could not remember being trained than in ROW, with some percentages sometimes being 2–3 times higher in India.

The Indian HCPs filling out the ITQ were asked to identify themselves. Table 13 shows that a much higher percentage of diabetes educators and specialist doctors filled out the ITQ forms in India than in ROW. Indian HCPs

Table 10 Frequency with which injection sites checked

| Frequency | % India (<i>N</i> = 867) | % ROW (<i>N</i> = 12,505) |
|---|------------------------------|-------------------------------|
| Routinely every visit | 19.6 | 28.3 |
| Once a year | 11.1 | 12.6 |
| Only if I complain of a problem at a site | 31.7 | 20.2 |
| I cannot remember my sites ever being checked | 37.6 | 38.9 |

Table 11 Last time patient given instructions or advice on injections

| Frequency | % India (<i>N</i> = 970) | % ROW (<i>N</i> = 9598) |
|---------------------------------|------------------------------|-----------------------------|
| Within the past 6 months | 42.9 | 37.4 |
| Within the past 6–12 months | 19.4 | 17.6 |
| Sometime in the last 1–5 years | 14.9 | 21.5 |
| Sometime in the last 5–10 years | 4.2 | 13.5 |
| Never | 18.6 | 10.0 |

were then asked if they were aware that there were new injection recommendations that had been published and 94.1% (64 of 68) said yes. Of these 92.3% (60 of 65) said they had changed their practice as a consequence of these recommendations.

DISCUSSION

Lipohypertrophy (LH)

LH is a thickened, “rubbery” lesion that appears in the subcutaneous (SC) tissue of injecting sites in up to half of patients who inject insulin. In some patients the lesions can be hard or scar-like [4, 5]. Detection of LH requires both visualization and palpation of injecting sites, as some lesions can be more easily felt than seen [6]. Making two ink marks at opposite edges of the LH (at the junctions between normal and “rubbery” tissue) will allow the lesion to be measured, recorded, and followed long-term.

More than a quarter of our Indian patients described lesions consistent with LH at their injection sites (Table 1) and approximately 1 in 5 were found to have LH by the examining nurse (using visual inspection and palpation) at the time of the ITQ (Tables 1, 2). Figure 1 illustrates visible LH in a woman who had injected in the same two locations below the umbilicus for 12 years. Figure 2 illustrates the detection of palpable LH by comparing a fold of normal skin (arrow tips close together) with lipohypertrophic tissue (arrow tips spread apart). Normal skin can be pinched tightly together, while lipohypertrophic lesions cannot [7].

LH in India is slightly less frequent than in ROW (Table 1). This may reflect the fact that Indian injectors have been using insulin only 5.5 years on average, while patients in ROW have been using it on average 9.0 years (Table 3 of our first ITQ paper [1]); or it may mean that intensive therapy with multiple daily injections (MDI) is still not common in India. (Both time on insulin and number of injections/day are known to be risk factors for LH.)

As in ROW, Indian HCPs who examined injection sites in our study found more LH lesions by palpation than visually (Table 2),

Table 12 Topics patients cannot remember ever being trained in

| Topic | % India (<i>N</i> = 988) | % Row (<i>N</i> = 8790) |
|---|------------------------------|-----------------------------|
| Injection sites (e.g., thigh, arm, buttock, abdomen) | 37.7 | 11.6 |
| Skin thickness and appropriate depth of injection | 57.2 | 27.2 |
| Length of needle | 57.2 | 25.6 |
| How to do a skinlift or “pinch up” the skin | 43.6 | 18.2 |
| How long to hold a skinlift or “pinch up” | 49.7 | 25.7 |
| Angle of needle entry | 37.9 | 16.1 |
| How long to keep the needle in the skin after injection | 43.5 | 16.4 |
| Rotating within an injection site | 48.7 | 18.4 |
| Prevention of air bubbles (syringe) or proper priming of pen needle | 52.0 | 19.7 |
| Mixing insulin in a syringe (for syringe users) | 53.2 | 30.3 |
| Re-suspension of cloudy insulin | 55.1 | 25.0 |
| Single use of pen needle/syringe | 61.0 | 19.0 |
| Safe disposal of sharps (pen needles, syringes) | 65.3 | 28.2 |

Table 13 Professional who filled out the ITQ

| Professional | % India (<i>N</i> = 72) | % ROW (<i>N</i> = 1263) |
|-------------------------------|-----------------------------|-----------------------------|
| General nurse | 9.7 | 17.1 |
| Diabetes nurse | 11.1 | 56.1 |
| Diabetes educator | 63.9 | 22.8 |
| Doctor (general practitioner) | 2.8 | 1.0 |
| Doctor (specialist) | 12.5 | 3.0 |

emphasizing the importance of carefully examining sites with the hands. HCPs should lubricate their hands before the exam with gel (ultrasound gel or equivalent) and use a circular motion, similar to that employed when examining the breast. LH lesions in India average about 40 mm, a size which is usually easy to detect, if one looks for it (Table 3).

Of some consolation is that Indian patients with LH do not inject into these lesions as frequently as in ROW (Table 4). When asked why they continued to do so, convenience and pain were less frequently cited by Indian patients

**Fig. 1** Two visible lipohypertrophic lesions below the umbilicus

than those in ROW (Table 5). Most patients simply did not know why they did so, suggesting that habit or mindlessness is at play.

Upwards of a quarter of Indian patients have LH. This should probably be considered an underestimate, since HCPs participating in the ITQ did not get any special training in LH detection. The prevalence rates of LH amongst insulin-injecting patients in other countries



Fig. 2 The different “pinch” characteristics of normal (*left*) vs lipohypertrophic (*right*) tissue

varies significantly. In five recent studies it ranged from lowest to highest: 14.5% (Hajheydari et al. [8]); 27.1% (Raile et al. [9]); 34.5% (Partanen and Rissanen [10]); 48.0% (Kordonouri et al. [11]); 64% (Blanco et al. [12]). Blanco et al. studied 430 patients from 19 Spanish centers and found that LH was more common in T1DM (72.3%) than in T2DM (53.4%). Grassi et al. [13] studied 388 patients from 18 Italian centers and found a prevalence of 48.7%. A Chinese study [14] of 401 patients in four centers found an overall prevalence of 53.1% (95% CI 48.2, 58.0%). By body site, LH was found in 52.4% of abdomens examined, 15.5% of thighs, and 9.4% of arms.

Lipohypertrophy has also been reported to be frequent in continuous subcutaneous insulin infusion (CSII) patients. A cross-sectional study [15] of 50 consecutive patients with T1DM using CSII for more than 6 months (26 female; age, 13.3 ± 3.5 years; CSII duration, 2.8 ± 1.7 years; HbA1c, $7.7\% \pm 1.1\%$) examined the skin for complications associated with therapy and 42% of these patients had LH. A similar survey [16] of 91 adult CSII patients revealed that the commonest infusion site problem was lipohypertrophy (26.1%), which occurred more often in those with long duration of CSII (4.8 [2.38–9.45] vs 3.0 [1.50–4.25] years; $p = 0.01$).

Vardar and Kizilci [17] identified, by logistic regression analysis, three independent risk

factors for LH: duration of insulin use, with longer use associated with more LH ($p = 0.001$); site rotation, with a failure to rotate associated with higher LH risk ($p = 0.004$); changing needles, with needle reuse also associated with LH ($p = 0.004$). Two other studies [12, 18] have identified similar factors. Immunologic factors in LH are poorly understood, although antibodies seem to have a role in pediatric and adolescent patients with T1DM [9]. Needle length has not been shown to be a risk factor. It is also not known what the impact of different needle lengths is on insulin absorption from injections into LH.

Histopathologically, LH lesions are shown to be entirely formed of adipocytes. These cells are often hypertrophied to two or three times the size of normal adipocytes. They can be seen invading the adjacent reticular dermis, engulfing lipid droplets, proliferating or manifesting other signs of metabolic activation [19]. This anabolic activity is presumably initiated by trauma from repeat injections in the same place and time coupled with the growth-promoting properties of insulin. There may be genetic factors but these have not yet been elucidated.

Almost all studies of patients injecting into LH [20–23] show insulin absorption to be delayed or erratic, potentially worsening diabetes management.

Franzen and Ludvigsson [24] evaluated children with diabetes who were injecting into clinically detectable LH. The children received simple but direct instructions: rotate injection sites; and do not reuse your needles. In 3 months 90% of LH lesions in these children had resolved and were undetectable. HbA1c was improved significantly and insulin requirements had decreased.

Blanco et al. [12] showed that unexplained hypoglycemia and glycemic variability were also greatly increased (6- to 7-fold) in those with versus those without LH. In our study we found that unexpected hypoglycemia affected more than a quarter of Indian injecting patients, while glucose variability was present in over a third. In both cases, these adverse outcomes were more common than in ROW (Table 6). Both have many causes, and injecting into LH is one of them.

A critical finding of a Spanish study is the correlation of total daily dose (TDD) of insulin to the presence of LH and its derived cost to the health care system. Subjects with LH had significantly higher TDD, overall and in both T1DM and T2DM groups. T2DM patients had the highest TDD differences (approximately 20 additional units daily). Such patients tend to have increased weight and insulin resistance compared to T1DM patients, and these factors probably contributed to their greater TDD; however, the T2DM patients with LH had similar weight and BMI as those with T2DM but without LH. Another major contributor is the practice of injecting into LH where the absorption properties of insulin are distorted. The cost of the additional insulin consumed by injecting into LH was calculated (based on prevalence of LH, number of insulin-injecting patients in Spain, differences in TDD, and the cost in Euros per unit of insulin) to be over 122 million euros in Spain. This is an obvious opportunity for savings to both patients and health care payers. The one weakness of the Spanish study is that HbA1c levels were unfortunately not collected from the subjects examined. A Chinese study similar to the Spanish one showed remarkably similar results,¹ with the addition that patients with LH had significantly higher HbA1c values (8.2 ± 1.8) than those without LH (7.7 ± 1.5) ($p < 0.003$) [14, 25].

The impact of LH on insulin PK-PD is rather poorly documented in the literature. While there are case reports indicating reductions in

insulin consumption with improvements in HbA1c when patients with LH were taught to inject into normal areas, and a small number of studies that evaluated insulin PK-PD when patients injected into areas of LH vs normal areas, the overall quality of such studies is poor and/or they were substantially underpowered. It is assumed that LH reduces and/or slows insulin uptake, and perhaps increases PK-PD variation, but this has not been proven rigorously.

Two closely related studies have addressed these questions, using state-of-the-art methodologies. A glucose clamp study [26] in patients with LH has shown that both insulin absorption and action are substantially blunted and considerably more variable when insulin is injected into areas with LH.² A separate, mixed meal study in the same subjects confirmed the slower absorption and decreased action of insulin when injected into LH compared to normal adipose tissue, with much greater post-meal glycemic excursions shown [27].

Site Rotation

Several studies have demonstrated that the best way to safeguard normal tissue is to properly and consistently rotate injecting sites [28–30]. Injection can be rotated from one body region to another (abdomen to thigh, to buttock, to arm) but it must be remembered that absorption characteristics change depending on the

¹ Specifically, LH was present in 52.9% of participants. Patients were an average of 59.6 (SD = 11.5) years old and took insulin for 5.6 (SD = 4.6) years, averaging 33.0 (SD = 18.4) U/day. HbA1c was 8.2% (1.8) and 7.7% (1.5), respectively, in those with and without LH ($p = 0.003$). LH was associated with higher daily insulin dose (38.1 vs 27.1 U, $p < 0.001$) and cost [the Chinese currency, the Renminbi (RMB 8.2 vs 5.8, $p < 0.001$)]. Those with LH averaged 2.3 (2.2) nodes, had higher frequency of pen needle (PN) reuse (median 13.0 vs 7.5, $p = 0.003$), and greater total 6-month direct costs (RMB 5506.9 vs 5258.0, $p = 0.037$). With 8.4 million insulin injectors in China, the estimated excess annual direct cost of LH is RMB 2.2 billion (\$360 million). Average pain scores (0–10) were higher if LH was present (2.7 vs 2.0, $p = 0.021$), if ≥ 3 nodes were present (3.8 vs 2.3, $p < 0.001$), and if PNs were not reimbursed (2.8 vs 1.7, $p < 0.001$). Patient satisfaction decreased as presence, number, and size of LH nodes increased (all $p < 0.05$).

² Specifically the study investigated insulin exposure and pharmacodynamics of insulin lispro injected into abdominal areas with LH or normal adipose tissue. Thirteen T1DM with LH (confirmed by palpation and ultrasound) received single doses of 0.15 U/kg LIS approximately every 6 h, twice into a region with LHT and twice into normal tissue. Comparing LHT with NAT injection, LS-mean INS concentrations were comparable during the first 30 min (AUCINS0–0.5 h 8.8 vs 9.4 h mU/L), but significantly lower thereafter (AUCINS0–1 h 29.3 vs 41.5 h mU/L, AUCINS.0–4 h 97 vs 154 h mU/L, all $p < 0.02$). Maximum INS exposure was reduced by 34% (CINSmax 49.7 vs 75.4 mU/L, $p < 0.002$). The PD effect in the first 4 h was 27% lower with LHT injection (AUCGIRO–4 h: 529 vs 720 mg/kg, $p < 0.05$), whereas maximum GIR was comparable (GIRmax 5.5 vs 6.0 mg/kg/min, $p = 0.378$). Intrasubject variability was substantially higher after dosing into LHT (coefficients of variation 52% vs 11% [AUCINS.0–4 h] and 57% vs 23%, [AUCGIRO–4 h], all $p < 0.002$).

type of insulin given. Analogues can be given at any injection site with similar uptake and action (PK-PD), but human insulins (regular, NPH) vary substantially—absorption being fastest from the abdomen and slowest from the buttock. However, correct rotation involves spacing injections a least 1 cm. apart even within an injection zone. Table 8 shows that 68.1% of Indian injectors were found to correctly rotate site, a value similar to ROW. This may be why the LH rate in India is lower than in ROW (Table 1).

Some clinicians are offering the single-use skin safe marker pen to patients to keep and use to make a dot on the skin where they inject and use this as a reference point for the next injection. This seems to work very well for some patients and the marker from the pen washes off and fades to nothing in about 5 days.

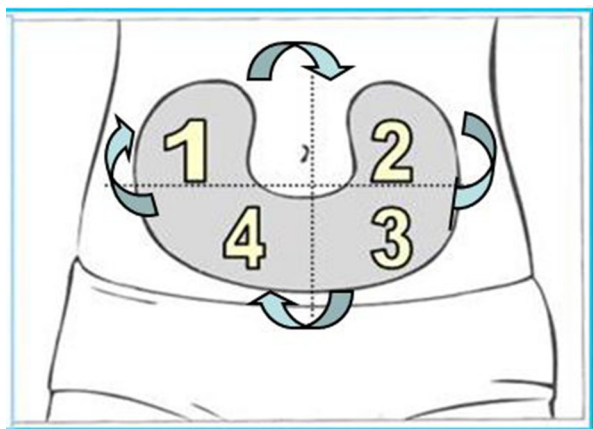


Fig. 3 Abdominal rotation pattern by quadrants

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, as shown by Figs. 3 and 4 [7]. Injections within any quadrant or half should be spaced at least 1 cm from each other in order to avoid repeat tissue trauma. Pump cannulae should be placed at least 3 cm away from previous sites. HCPs should verify that the rotation scheme is being followed at each visit and give help and advice where needed.

Lipoatrophy

Lipoatrophy (LA) has been reported in all injecting sites [31–36]. It is now considered a relatively unusual condition, prompting case reporting. Risk factors are not understood. Some authors have suggested that young women with other autoimmune disorders may be at higher risk. LA is felt to be a local immune reaction against fat cells provoked by insulin crystals. Consequently LA is rarer today than it was when less pure insulins were given. But LA is still observed even with short- and long-acting analogues. LA causes significant variability in insulin absorption when injections are given into it.

Treatment for LH is not evidence-based because of the lack of trials. Several approaches, however, have been recommended: changing the insulin formulation (e.g., aspart to lispro, or lispro to glulisine, etc.), changing injection sites, or shifting to CSII and possibly cortisone injected into the LA. LA may or may not resolve

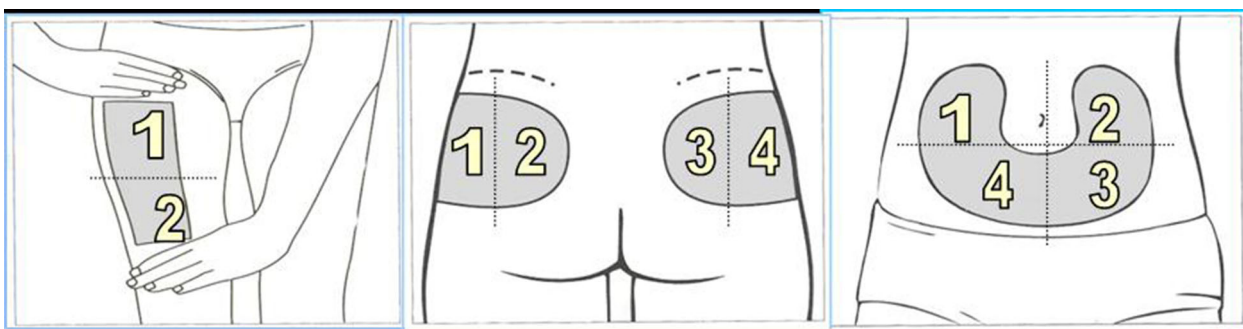


Fig. 4 Thigh and buttocks rotational pattern by halves

with time, but this depends on the individual patient. LA has been seen with the short-acting analogues, lispro and aspart, as well as the long-acting ones, glargine and detemir. It may also be associated with non-rotation of injection sites and needle reuse. LA is both a cosmetic problem (disfiguring) and a clinical one (erratic and abnormal insulin absorption).

Fortunately lipoatrophy is now much less common than it used to be in the days of animal insulins. In our study it affected only about 2% of Indian injectors, a figure compatible with ROW (Table 7).

Injection Pain

We found that just over half of Indian injectors report having pain on injection. Of these, 4 out of 5 report having painful injections only several times a month or year (i.e., not with every injection).

As the above data suggests, 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. Patient awareness of injection discomfort has been studied extensively and is related to three key factors: needle length (and tissue level penetrated); needle diameter; and injection context. Injection context is defined by environment (including noise and the presence of other people), view of the needle, and the apprehension of HCPs, both professional and family. The more apprehension the latter display, the greater the pain and anxiety felt by the patient [37, 38]. This reverse transference places a large responsibility on carers to assess their own attitudes towards injection pain. Some patients complain of discomfort when injecting insulins which have a low pH. This seems, anecdotally, to be reported more commonly in children. Glargine is an example of an acidic insulin.

Heise et al. [39] showed that injection speed (150, 300, and 450 $\mu\text{l/s}$; equivalent to 15–45 IU/s of U100 insulin) makes no difference in pain. But injection volume does, with higher volumes ($\geq 1200 \mu\text{l}$ or 120 IU of U100 insulin) causing

more pain. His group also found that injections in the thigh appear to hurt more than those in the abdomen in adults. Anderson et al. [40] and Jorgensen et al. [41] also found that higher injected volumes cause more pain. Hofman et al. [42] as well showed in both children and adults that thigh injections are more painful than abdominal ones. Nevertheless, Heise et al. [39] found that most patients say the pain is acceptable regardless of volume or injection site. So we can reasonably conclude that injection pain, though felt under certain circumstances by certain patients, is mild enough to be acceptable to most of them, particularly with today's very thin, short needles.

This survey shows that at present injection training in India is performed mainly by diabetes educators and physicians (Table 9). Despite this specialized approach, a very high percentage of patients report that they have not been trained (at least cannot remember being trained) in a wide range of essential injection topics (Table 12).

The latest version of the Indian insulin injection recommendations (from 2015 [43]) has specific guidelines for each one of these topics, and many others.

We know that injecting training works, even when delivered only one time. In a recent Italian study [13], 346 patients with diabetes from 18 ambulatory centers throughout northern Italy who had been injecting insulin for at least 4 years received a thorough evaluation of their injection technique (IT). Their doctors and nurses then examined all injection sites for the presence of LH, followed by an individualized training session in which suboptimal IT practices were addressed. All patients were taught to rotate sites correctly in order to avoid LH and were begun on 4-mm pen needles to increase potential injection sites, while avoiding intramuscular (IM) injections. Patients were also instructed not to reuse needles. Results showed that 49% of patients had LH at study entry. After 3 months, patients had mean reductions in HbA1c of 0.58%, in fasting blood glucose of 14 mg/dL, and in total daily insulin dose of 2.0 IU (from baseline 50.5 IU), all statistically significant at $p < 0.05$. Follow-up questionnaires showed that significant numbers of patients

recognized the importance of IT and were performing their injections more optimally. The majority found the 4-mm pen needle convenient and comfortable.

The relationship between diabetes education and glucose control is far from simple. A recent study suggested that education alone (including empowerment) may not be sufficient to ensure behavioral change and improved glycemic control, at least in T2DM patients managed in primary care [44].

Therapeutic Education

It is clear that “education”, defined as the simple imparting of information, is not enough. In diabetes we must employ “therapeutic education” [45]. Therapeutic education is above all patient-centered, focusing on individual needs, resources, and values. It tailors individual strategies to the patient, and the individual patient helps shape these strategies. Patients participate actively in their treatment, eventually virtually taking it over. Therapeutic education takes into account a whole array of psychological, social, and biologic factors. It tackles the hardest things human beings must do—change behavior. It uses the approaches and brings to bear all power of cognitive behavioral therapy. It focuses on motivation, step-by-step change, and compassion with oneself in the face of failure. Injection training must be rooted in therapeutic education to be effective.

Studies have shown that not all patients receive therapeutic education about injections and for those who do, not all critical topics are covered [46–48]. This was very clear from our study (Table 12). One principle of therapeutic education is that decisions should be made in a discussion context in which the patient is a partner and the HCP offers experience and advice [49, 50]. Therapeutic education can also occur in a group setting, and there is evidence that lower subsequent HbA1c values and better adherence are achieved if the HCP has formal training as an educator [6].

Educational guidelines for injectors recommend checking injection sites at least

annually and more frequently when the risk for LH or other complication is high. Our study showed that only about 30% of Indian injectors get their sites checked this frequently (Table 10), with nearly a third only having sites checked when they specifically complained and nearly 4 out of 10 never having had their sites checked. This is clearly an area in which therapeutic education in India can be improved.

Conversely, India is doing a somewhat better job than ROW in giving advice about injections. Nearly two-thirds of injecting patients had been given instruction in the last year (Table 11). But Indian HCPs can clearly do a better job covering all the vital topics essential to proper injection habits (Table 12).

CONCLUSIONS

The first Indian insulin injection technique recommendations were published in *Indian Journal of Endocrinology & Metabolism*, November 2012 issue. Addenda were published in the November 2013 and November 2014 issues of that journal. The latest version of these recommendations were published in 2015 [43]. That version provides the following guidelines for preventing LH:

- Regular inspection and palpation of insulin sites
- Do not reuse needles
- Follow correct site rotation policy
- Use larger injection surface areas
- Do not inject into LH sites
- Reduce dose of insulin in habitual LH site injections when shifting to normal SC tissue
- Rule out LH as a cause of poor glycemic control, hypoglycemia, and high glycemic variability

Before starting the injection therapy, the healthcare provider should ensure that patients understand each of these essential topics:

- The injection regimen
- The choice and management of the devices used
- The choice, care, and self-examination of the devices used

- Proper injection techniques (including site rotation, injection angle, and possible use of skinfolds)
- Injection complications and how to avoid them
- Optimal needle lengths
- Safe disposal of used sharps [6, 49–55]
- *Healthcare professionals should spend ample time* exploring patient anxieties and other concerns about the injecting process and insulin itself.

A quality management process should be put in place and make sure that the correct injection technique has been practiced regularly by patients and is also documented in the record.

All results from the ITQ survey data are available in an interactive form on Tableau Public Adam Young's Profile website [56]. We believe the latest ITQ data support and reinforce the above recommendations. Every diabetes center in India should be familiar with the ITQ results and should be scrupulous in following the official Indian insulin injection recommendations.

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Data Availability. All results from the ITQ survey data are available in an interactive form on Tableau Public Adam Young's Profile website [56].

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