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Worldwide Injection Technique Questionnaire Study: Injecting Complications and the Role of the Professional

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Abstract

From February 1, 2014, through June 30, 2015, 13,289 insulin-injecting patients from 423 centers in 42 countries participated in one of the largest surveys ever performed in diabetes. The first results of this survey are published elsewhere in this issue. Herein we report that the most common complication of injecting insulin is lipohypertrophy (LH), which was self-reported by 29.0% of patients and found by physical examination in 30.8% by health care professionals (HCPs). Patients with LH consumed a mean of 10.1 IU more insulin daily than patients without LH. Glycated hemoglobin levels averaged 0.55% higher in patients with vs without LH. Lipohypertrophy was associated with higher rates of unexplained hypoglycemia and glycemic variability as well as more frequent diabetic ketoacidosis, incorrect rotation of injection sites, use of smaller injection zones, longer duration of insulin use, and reuse of pen needles (each $P<.05$). Routine inspection of injection sites by the HCP was associated with lower glycated hemoglobin levels, less LH, and more correct injection site rotation. Patients were also more likely to rotate correctly if they received injection instructions from their HCP in the past 6 months. Fewer than 40% of patients claimed to have gotten such instructions in the past 6 months, and 10% said that they have never received training on how to inject correctly despite injecting for a mean of nearly 9 years. Use of these data should stimulate renewed commitment to optimizing insulin injection practices.

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In a separate article in this issue we introduce the worldwide Injection Technique Questionnaire (ITQ) survey.[1] That article describes the patient population and its injecting practices as well as survey methods, materials, centers, and participants. The present article addresses injection-related complications and the role of the health care professional (HCP).

RESULTS

Lipohypertrophy

To assess the presence of 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)?" Overall, 29.0% answered yes. Nurses were asked to examine all the injection sites for LH both visually and by palpation. They found LH in 30.8% of patients; the frequencies by site and type of examination are shown in Table 1. The frequency of LH was relatively consistent across the 42 countries surveyed. Lipohypertrophy was seen almost twice as frequently in patients with type 1 diabetes mellitus (T1DM) as in those with type 2 diabetes mellitus (T2DM) and was virtually absent in patients with gestational diabetes, probably because of the very short time that such patients have been using insulin (data not shown).

Although there was a correlation between LH lesions that were visible and those that were palpated, it was not 100%. Table 2 presents data on this correlation in abdominal LH (the most frequent site used and consequently the one most frequently reported as having LH). Eighty-four percent of LH could be both seen and felt, but 14% could be felt but not seen. The same pattern is seen with the thigh, buttock, and arm (data not shown).

TABLE 1. Findings From Visual and Palpation Examination by Nurses for Lipohypertrophy by Site

Injection site	Examination type	Lipohypertrophy found (%)[a]
Abdomen (n=7565)	Visual	17.3
	Palpation	21.1
Thigh (n=5425)	Visual	9.8
	Palpation	11.2
Buttock (n=2566)	Visual	2.1
	Palpation	2.8
Arm (n=4204)	Visual	11.2
	Palpation	13.4

[a]Overall, the nurses found lipohypertrophy in 30.8% of patients.

When nurses found LH they were asked to measure the lesion along its longest axis. Results are shown in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).[2] Lesions of LH varied from a mean of approximately 35 mm (in the arm) to approximately 50 mm (in the buttock), but there was considerable variability around these averages. When nurses found LH they asked the patient whether they were still injecting into it, and 44.0% said yes. Patients still injecting into LH were then asked how often they were doing so and why (Table 3).

Lipohypertrophy is associated with giving more injections per day, an earlier age at diagnosis of DM (especially in T1DM), and a longer number of years with DM and taking insulin (each $P<.05$). We found no association between the presence of LH and body mass index. Just less than one-third of those taking glucagon-like peptide-1 receptor agonists were found to have LH, but there was no association between LH and the duration of this therapy. It is unclear whether LH predated glucagon-like peptide-1 receptor agonist therapy.

TABLE 2. Correlation Between Visible and Palpable Findings of Abdominal Lipohypertrophy[a]

	Visible (No. [%])	
Palpable	No	Yes
No	5112	23 (2)
Yes	186 (14)	1102 (84)

[a]A total of 6423 patients' abdomens were examined. Percentages are based on the 1311 patients with lipohypertrophy.

TABLE 3. Injections Into Lipohypertrophy

Parameter	Patients (%)
Frequency (n=1964)	
Every injection	16.7
Frequently (daily)	39.5
Occasionally (weekly)	30.3
Seldom (monthly)	13.5
Reason (n=1866)	
Convenient	16.8
Less painful	22.1
Just a habit	34.7
Do not know	26.4

There was a strong association between the presence of LH and the total daily dose (TDD) of insulin (Table 4). A mean of 10.1 IU more insulin was consumed in the population with LH compared with those without LH. In patients with T2DM, this average TDD difference rose to 13.5 IU, whereas in patients with T1DM, the average TDD difference was 5.4 IU. These differences were similar in patients with LH who continued to inject into LH vs those who did not (Table 4).

Similar differences were seen for the various types of insulin: fast-acting analogues (mean of 4.4 IU more in patients with LH vs those without), basal analogues (mean of 1.5 IU more), and premixes (mean of 9.8 IU more) (all differences significant at $P<.05$). All currently used families of insulins were associated with LH (ie, there are no insulins that seem to protect the user from LH). However, it is not possible by the present data to determine whether any one type of insulin has higher risks.

The presence of LH was associated with higher glycated hemoglobin (HbA_{1c}) values,

TABLE 4. TDD of Insulin as a Function of LH[a]

Parameter	TDD (IU), mean ± SD	Patients (No.)
LH present		
Yes[b]	55.2±33.0	2192
No	45.1±31.5	4889
Total	48.2±32.3	7081
Injecting into LH		
Yes[b]	56.1±33.2	1644
No	47.1±32.2	2064
Total	51.1±32.9	3708

[a]LH = lipohypertrophy; TDD = total daily dose.
[b]Differences "Yes" vs "No"; significant at $P<.001$.

TABLE 5. Association of Lipohypertrophy With HbA_{1c} Levels[a]

Lipohypertrophy	HbA_{1c} (%), mean ± SD	Patients (No.)
Yes[b]	8.85±2.7	2205
No	8.30±1.9	4795
Total	8.47±2.2	7000

[a]HbA_{1c} = glycated hemoglobin.
[b]Differences "Yes" vs "No"; significant at $P<.001$.

TABLE 6. Association of Needle Reuse With Lipohypertrophy (n=3295)

	Lipohypertrophy (%)	
Needle reuse	Yes	No
2 times	33.9	66.1
3-5 times	35.1	64.9
6-10 times	34.6	65.4
>10 times	43.8[a]	56.2[a]

[a]Difference significant compared with the other values in the column at $P<.001$.

with a mean HbA_{1c} level 0.55% higher in patients with LH than in those without LH (Table 5). These differences were almost the same for patients with T1DM as for those with T2DM. Lipohypertrophy was associated with higher rates of unexpected hypoglycemia and glycemic variability as well as more frequent diabetic ketoacidosis. (Data not shown but all differences were significant at $P<.05$.)

Lipohypertrophy was associated with incorrect rotation of injection sites, use of smaller injecting zones, longer duration of insulin use, and reuse of pen needles (all significant at $P<.05$). The higher the number of times the pen needle was reused, the more frequently LH was reported (Table 6). The size of the LH was also related to the number of times the needle was used (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).[2] Using logistic regression analysis, incorrect rotation and years taking insulin were shown to be the most important factors associated with LH ($P<.001$), and pen needle reuse remained significantly, but slightly less strongly, associated ($P=.02$).

Rotation of Injection Sites

Overall, 83.9% of injectors claimed to rotate injection sites; of these, 70.6% were found by nurses to be rotating correctly. Correct injection site rotation is defined as always injecting at least 1 cm from a previous injection. Those who rotate correctly were found to have less LH, less hyperglycemia, less unexplained hypoglycemia, and lower glucose variability. (Data not shown but each difference was significant at $P<.05$.) Mean levels of HbA_{1c} were 0.57% lower in those who correctly rotate (Table 7). Correct rotation was also associated with 4.7 IU lower TDD (Table 7). When the HCP checked sites routinely, this practice was associated with lower HbA_{1c} levels, less LH, and more correct rotation. Patients were also more likely to rotate correctly if they received injection instructions in the past

TABLE 7. Association of Correct Injection Site Rotation With HbA_{1c} Levels, TDD of Insulin, and Needle Length[a]

	Correct rotation		
Parameter	Yes	No	Total
HbA_{1c}			
%, mean ± SD	8.28±1.79	8.85±2.01	8.44±1.87
Patients (No.)	5187	2123	7310
TDD			
IU, mean ± SD	47.2±31.8	51.9±33.1	48.6±32.3
Patients (No.)	5220	2164	7384
Needle length (%) (n=7185)			
4 mm	76.3[b]		
5 mm	71.1		
6 mm	71.6		
8 mm	63.9[c]		

[a]HbA_{1c} = glycated hemoglobin; TDD = total daily dose.
[b]Difference significant compared with the other needle length values at $P<.001$.
[c]Difference significant compared with the other needle length values at $P<.001$.

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TABLE 8. Association of Injection Pain With Bleeding and Needle Reuse

Parameter	Pain	
	Yes	No
Bleeding (%) (n=9061)		
Yes	42	18
No	13	27
Needle reuse (n=3771)[a]		
2 times	52.4	
3-5 times	55.1	
6-10 times	59.5	
>10 times	62.9	

[a]Individual percentages in each row are significantly different from the values in each row below at $P < .001$.

6 months. Correct rotation seems to increase in frequency as the needle shortens (Table 7), although this may be a by-product of the level of education and training given when switching patients to such needles.

Bleeding and Bruising

Patients were asked whether they saw bleeding or bruising from their injection sites, and 60.2% reported that they did. They were also asked about the frequency of bleeding or bruising, and only 0.5% said always, 7.3% said often (several times a week), 41.5% said sometimes (several times a month), and 50.8% said almost never (several times a year).

Pain

Just more than half of the injectors reported having pain on injection. Of these, 84.5% report having painful injections only several times a month or year (ie, not with every injection). Groups with a higher frequency of reported pain were patients with T1DM, children, adolescents, and women. (Data not shown but all differences were significant at $P<.05$.) Pain was commonly associated with bleeding (Table 8). Pain is also associated with several other factors, without obvious causative relationships: injecting through clothes, injecting insulin while it is still cold (just out of the refrigerator), hypoglycemia and hyperglycemia, LH, injecting into LH, incorrect site rotation, higher HbA_{1c} levels, lower body mass index, younger age, and higher TDD of insulin. (Data not shown but each difference was significant at $P<.05$.) Pain is also associated with needle reuse and seems to increase as a function of the number of times the needle is reused (Table 8).

TABLE 9. Frequency of Lipoatrophy and Redness by Injection Site

Injection site	Finding	Patients (%)
Abdomen (n=7565)	Lipoatrophy	0.6
	Redness	3.3
Thigh (n=5425)	Lipoatrophy	0.5
	Redness	2.8
Buttock (n=2566)	Lipoatrophy	0.2
	Redness	0.4
Arm (n=4204)	Lipoatrophy	0.4
	Redness	3.6

Lipoatrophy and Inflammation

Nurses also examined each injection site for the presence of lipoatrophy and redness (Table 9). Both of these were reported at a much lower frequency than LH.

Insulin Leakage

Overall, 36.9% of patients reported leakage or backflow of insulin from the skin. Of these, 84.5% reported that the occurrence was rare (several times a month or a year). Leakage occurred more frequently in patients with T1DM than in those with T2DM. Leakage seemed to be more frequent in patients who had LH or who injected into LH, did not leave the pen needle under the skin for 10 seconds after injecting, or did not rotate injection sites correctly (Table 10).

The longer that pen users left the needle under the skin after the plunger was pushed in (and especially if they reached the 10-second goal), the less frequently leakage was reported.

TABLE 10. Association of Leakage From the Skin With Time That the Needle Is Under the Skin and TDD of Insulin[a]

Parameter	Leakage		Total
	Yes[b]	No	
Dwell time (No. [%])			
Not aware how long	142 (42.9)	189 (57.1)	331 (100.0)
<5 s	649 (40.9)	936 (59.1)	1585 (100.0)
5-10 s	1512 (38.7)	2394 (61.3)	3906 (100.0)
>10 s	974 (35.7)	1751 (64.3)	2725 (100.0)
TDD of insulin			
IU, mean ± SD	51.8±32.2	46.6±32.5	48.5±32.4
Patients (No.)	2819	4777	7596

[a]TDD = total daily dose.
[b]Each percentage is a significant decline compared with the previous percentage at $P<.001$.

TABLE 11. Frequency of Professional Intervention

Intervention and frequency	Patients (%)
Injection site inspection (n=12,505)	
Routinely at every visit	28.3
Once a year	12.6
Only if I describe a problem at a site	20.2
I can't remember my sites ever being checked	38.9
Date patient was last given instructions on injection (n=9598)	
Within the past 6 mo	37.4
Within the past 6-12 mo	17.6
Sometime in the past 1-5 y	21.5
Sometime in the past 5-10 y	13.5
Never	10.0

Patients with leakage used, on average, 5.2 IU more insulin a day (Table 10).

Role of HCPs

Identification of HCPs can be found in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org)[2] and areas of practice influenced by the new recommendations in Supplemental Table 4 (available online at http://www.mayoclinicproceedings.org).[2] Patients were asked who had given them their injection training. Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org)[2] shows that most frequently it was their diabetes nurse. The frequency of HCP injection site inspection as reported by patients is shown in Table 11. Approximately 28% said that site inspection was routinely performed at each visit, but nearly 39% said that they could not remember it ever being performed. The last time patients reported receiving instruction or advice on injections is provided in Table 11.

TABLE 12. Injection Topics That Patients Could Not Remember Ever Being Trained on (n=8055)

Topic	Patients (%)
Injection sites (eg, thigh, arm, buttock, abdomen)	11.6
Skin thickness and appropriate depth of injection	27.2
Length of needle	25.6
How to do a skin lift or "pinch up" the skin	18.2
How long to hold a skin lift or "pinch up"	25.7
Angle of needle entry	16.1
How long to keep the needle in the skin after injection	16.4
Rotating within an injection site	18.4
Prevention of air bubbles in syringes or proper priming of pen needles	19.7
Mixing insulin in a syringe (for syringe users)	30.3
Resuspension of cloudy insulin	25.0
Single use of pen needles/syringes	19.0
Safe disposal of sharps (pen needles/syringes)	28.2

They were also asked what injection topics they could not remember ever being trained on (Table 12). Table 13 presents a comparison of various parameters among the most recent ITQ and the two previous ones. For implications, see the "Discussion" section.

Checking Injection Sites

In the current ITQ, the inspection by HCPs of injection sites was clearly related to the kind of patient being cared for (Supplemental Table 6, available online at http://www.mayoclinicproceedings.org).[2] The younger the patient, the more likely that sites were being checked routinely. The frequency of checking sites was also related to who delivered the injection training (Supplemental Table 7, available online at http://www.mayoclinicproceedings.org),[2] with diabetes nurses having the best record in this regard. Patient HbA_{1c} levels also differed according to who gave the injection training, with the lowest HbA_{1c} values associated with training delivered by a diabetes nurse (Supplemental Table 8, available online at http://www.mayoclinicproceedings.org).[2]

The frequency of inspecting injection sites did not vary from males to females or from syringe users to pen users but was considerably more frequent in adolescents and children than in adults. More than 70% of patients with gestational diabetes had their sites checked routinely, whereas less than half of patients with T1DM did and only approximately a quarter of patients with T2DM. Most diabetes nurses checked sites routinely, whereas others (including diabetes specialist doctors) rarely did. Checking sites routinely was associated with lower HbA_{1c} levels, less LH, and more correct rotation. Patients were also more likely to rotate correctly if they received injection instruction in the past 6 months. Furthermore, more recent instruction is associated with lower levels of needle reuse and fewer hospitalizations for hypoglycemia. (Data not shown but all differences were significant at $P<.05$.)

DISCUSSION

Nearly a third of the participants described lesions consistent with LH at their injection sites, and approximately the same proportion were found to have LH by the examining nurse (using visual inspection and palpation). One clue to the presence of LH is that normal

skin can be pinched tightly together, whereas LH lesions cannot. In addition, LH often has a rubbery texture or is felt as a "step up" when palpating injection sites with lubricated fingers (using ultrasound gel or an equivalent).

The prevalence rates of LH in insulin-injecting patients with DM in 5 studies are, from lowest to highest: 14.5% (Hajheydari et al, 2011),[3] 27.1% (Raile et al, 2001),[4] 34.5% (Partanen and Rissanen, 2000),[5] 48.0% (Kordonouri et al, 2002),[6] and 64% (Blanco et al, 2013).[7] In the 2009 ITQ,[8] 48% of the more than 4200 patients answered "yes" to the following question (acknowledged to be somewhat nonspecific): "Have you ever noticed swelling of fatty tissue or small bumps at your injection sites?" The percentages in the 16 countries surveyed in that ITQ ranged from 30% to 88%. Several earlier surveys[5,9-11] reported similar findings. Note, however, that the wording of this question in the earlier ITQ is very different from the wording in the current ITQ: "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)?" (2014-1015 version). The earlier wording permits a wider time window and gives a less specific definition of LH than the wording in the latest ITQ. The fact that the most recent prevalence values (~30%) are lower than those in the 2009 ITQ (48%) is almost certainly a function of that nonspecific earlier wording and not of an actual reduction in LH worldwide (Table 13).

Glycated hemoglobin values were approximately 0.5% higher in injectors with LH than in those without LH (in both T1DM and T2DM) and are significantly higher with incorrect rotation of sites and frequent needle reuse, 2 practices that should be remediable through effective education/training. Most diabetes experts agree that a 0.5% difference in HbA_{1c} levels is significant. If a reduction in LH can lead to sustainable declines of this magnitude, a significant decrease in complications as well as in health care costs may be achieved.

The frequencies of unexpected hypoglycemia and glucose variability are significantly higher with the presence of LH, with injecting into LH, with incorrect rotation of sites, and with needle reuse. These findings are consistent with impaired and variable insulin absorption and action when injected into LH tissue, recently demonstrated in high-quality clamp and mixed meal crossover studies.[12,13] Having LH and injecting into LH are both associated with the consumption of more insulin leading to higher health care system costs, coupled with worse outcomes.[7] There is clearly much that can be done to reduce the frequency of LH, particularly through correct rotation of injection sites. Such reductions should improve clinical outcomes, reduce insulin consumption, and, thereby, lower costs.

It is increasingly apparent that proper injection technique is essential to good diabetes management. It may be as important as the choice and dose of insulin because the insulin will not work effectively unless injected properly. The

TABLE 13. Comparison of the Results of the Last 3 ITQ Surveys[a]

Parameter	ITQ survey		
	1999-2000	2008-2009	2014-2015
Participants (No.)	1002	4352	13,289
Participating centers (No.)	22	171	423
Countries (No.)	7	16	42
Age of participants (y), mean	47.0	48.4	51.9
Duration of therapy (y), mean	14.7	13.9	13.2
BMI of participants (mean)	26.5	27.3	26.6
Glycated hemoglobin (%), mean	8.0	8.1	8.5
Participants taking ≥4 injections per day (%)	46.2	43.9	44.9
Participants using insulin pens (%)	78.8	92.3	89.6
Length of needle used (%)			
8 mm	55.0	48.6	29.2
<8 mm	9.5	44.4	70.8
>8 mm	35.5	7.0	0.9
Injection site (%)			
Abdomen	85	88	90.9
Thigh	69	59	43.0
Buttock	24	16	13.8
Arm	34	29	31.9
Participants injecting using pinch up (%)	69.4	72.9	63.7
Rotation of injection sites (%)	38	91	83.9
Occasional bleeding or bruising (%)	62	61	60.2
Lipohypertrophy (%)	29	48[b]	30.8[cd]
Times a single needle used (mean)	3.3	3.6	[d]
Injection sites checked at every office visit (%)	22	36	28
Needles disposed into trash directly (%)	47	38	55
Needles disposed into trash without recapping (%)	22	3.5	6.9
Participants desiring more education on injection technique (%)	70	25	[d]

[a]BMI = body mass index; ITQ = Injection Technique Questionnaire.
[b]Patient reported (nurse found lipohypertrophy in 24%).
[c]Nurse found.
[d]Question posed differently than in previous surveys.

specialist diabetes nurse has a primary role in educating the patient on all aspects of injecting. In almost every country surveyed by the ITQ, this nurse is the primary guide and trainer for injections, although other HCPs often participate. Finally, the ITQ shows that it pays to check injection or infusion sites regularly, meaning ideally every visit but at a minimum yearly. The same is true of insulin delivery instruction. It should be given simultaneously with site inspection.

We also developed an Internet tool that allows users to query the ITQ database directly and to obtain infographics based on these queries. It is available in an interactive form on Tableau Public Adam Yeung's Profile website.[14] Use of these data should stimulate renewed interest in and commitment to optimizing insulin delivery practices in patients with diabetes.

CONCLUSION

This ITQ involving more than 13,000 patients from 42 countries is one of the largest surveys conducted in diabetes. Its scope covers injection practices from beginning to end: choice of device through to disposal. It elucidates the common habits that patients practice and the complications and other obstacles they face. Only in this manner can practical and targeted recommendations be made. A new set of insulin delivery recommendations has been developed and is also published in this issue.[15] Individual countries and local regions should revise and publish their own ITQ findings as well as insulin delivery guidelines in light of the new recommendations and the worldwide ITQ survey data reported herein.

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Our sincerest thanks to the 423 centers in 42 countries throughout the world (see Supplemental Table 9, available online at http://www.mayoclinicproceedings.org)[2] for opening their doors and hearts to the ITQ survey. The thousands of professionals and the 13,289 patients who participated have given an invaluable gift to the world of diabetes and medicine. We salute them.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **HbA_{1c}** = glycated hemoglobin; **HCP** = health care professional; **ITQ** = Injection Technique Questionnaire; **LH** = lipohypertrophy; **T1DM** = type 1 diabetes; **T2DM** = type 2 diabetes; **TDD** = total daily dose

Potential Competing Interests: Drs Hirsch, Morel, and Strauss are employees of BD, a manufacturer of injecting devices.

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