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ORIGINAL RESEARCH

Prevalence, Risk Factors, and Clinical Characteristics of Lipodystrophy in Insulin-Treated Patients with Diabetes: An Old Problem in a New Era of Modern Insulin

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Yotsapon Thewjitcharoen[1]
Hussamon Prasartkaew[1]
Phatharaporn Tongsumrit[1]
Saruda Wongjom[1]
Chatnapa Boonchoo[1]
Siriwan Butadej[1]
Soontaree Nakasatien[1]
Krittadhee Karndumri[1]
Veekij Veerasomboonsin[2]
Sirinate Krittiyawong[1]
Thep Himathongkam[1]

[1]Diabetes and Thyroid Center, Theptarin Hospital, Bangkok, Thailand; [2]Department of Radiology, Theptarin Hospital, Bangkok, Thailand

Background: Lipodystrophy has been reported as a common complication in insulin-treated patients, which could lead to unexplained hypoglycemia and suboptimal glycemic control. This study aimed to determine the prevalence, associated risk factors, and clinical characteristics of insulin-induced lipodystrophy in Thai patients.

Patients and Methods: This was a cross-sectional study involving insulin-treated patients at Theptarin Hospital, one of the largest diabetes centers in Thailand.

Results: A total of 400 patients were studied (female 53.5%, T2DM 86%, mean age 65.6 ±15.4 years, duration of diabetes 23.0±10.2 years, median insulin treatment 10 years, usage of insulin analog 72.1%, A1C 7.9±1.6%) . The prevalence of lipohypertrophy (LH) in overall patients was 37.3% (T1DM 46.4% and T2DM 35.8%). The highest prevalence (57.5%) was observed in long-standing (≥10 years) T1DM patients. Multivariate analysis revealed that the duration of insulin use (≥10 years), use of human insulin, and incorrect rotation of injection sites were associated with LH. Patients with LH were found to have 7-times greater risk of unexplained hypoglycemia when compared with patients without LH. Lipoatrophy (LA) was found in only four cases (1.0%). All LA cases had a concurrence palpable area of LH.

Conclusion: Insulin-induced lipodystrophy is still an overlooked complication in the conundrum of diabetes care. The presence of lipodystrophy was significantly associated with the occurrence of unexplained hypoglycemia. It should be emphasized to recognize this condition by inspecting and palpating insulin injecting sites regularly, and educate patients to avoid the development of lipodystrophy.

Keywords: lipodystrophy, lipohypertrophy, lipoatrophy, insulin, Thai

Introduction

Since the discovery of insulin in the last century, a variety of insulin analogs are available to mimic the action of endogeneous insulin. While insulin therapy is the choice of treatment for people with type 1 diabetes mellitus (T1DM), most people with long-standing type 2 diabetes mellitus (T2DM) will eventually require insulin therapy in their lifetimes as their diabetes progresses. Currently, it is estimated that 20–25% of all people with T2DM use insulin therapy.[1] Unfortunately, the importance of insulin injection technique and awareness of insulin-induced lipodystrophy is still an overlooked complication in the conundrum of diabetes care. Previous data from all over the world consistently demonstrated that there is a wide gap between

Correspondence: Yotsapon Thewjitcharoen
Diabetes and Thyroid Center, Theptarin Hospital, Bangkok, Thailand
Tel +66-2-348-7000
Email kamijoa@hotmail.com

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the current practices of insulin injection technique and the guideline recommendations.[2–5] Moreover, the awareness of insulin-induced lipodystrophy is inadequate among the healthcare personnel.[6]

Insulin-induced lipodystrophy has been classified into two major subtypes – lipohypertrophy and lipoatrophy. Insulin-induced lipohypertrophy (LH) remains a frequent complication of insulin injection, which has been reported as 49% in people with insulin-treated T2DM and 34% in people with T1DM in a recent meta-analysis.[7] Nevertheless, some previous data suggested that LH is more common in people with T1DM.[8] LH does not only cause cosmetic problems but also impairs the absorption of insulin which could lead to unexplained hypoglycemia and suboptimal glycemic control.[9,10] At the other end of the spectrum of insulin-induced lipodystrophy is lipoatrophy (LA) which is related with immune reaction.[11] It has rarely been found since the introduction of recombinant insulin in the 1980s.[12] However, concurrent occurrence of LH and LA in the same patient had been occasionally reported even in patients with the use of insulin analogs.[13,14] Therefore, healthcare professions should examine insulin injection sites in their insulin-treated patients periodically to early detect these cutaneous complications.

Though insulin-induced lipodystrophy is a well-recognized side-effect from insulin injection technique, there is still a dearth of information in Southeast Asia. Previous studies from various countries revealed that errors in insulin injections among insulin-treated patients were frequent; especially failure in the rotation insulin injection site which is one of the major causes of LH.[3–5,15] The present cross-sectional study aimed to determine the prevalence, associated risk factors, clinical characteristics of insulin-induced lipodystrophy, and awareness of this condition from their treating physicians in a series of insulin-treated patients from a tertiary diabetes center in Thailand.

Patients and Methods

All consecutive cases of insulin-treated patients attending diabetes clinic for a routine visit were recruited from June 2018 to March 2019 at Theptarin Hospital which is one of the largest diabetes centers in Thailand. Consecutive patients with T1DM or T2DM, attending the diabetes clinic for a routine visit were interviewed by using a structured questionnaire (Supplementary material) focusing on key insulin injection parameters and asked about the occurrence of unexplained hypoglycemic episodes in the previous 3 months. Severe hypoglycemia was defined according to a joint position statement of the American Diabetes Association (ADA) and International Hypoglycemia Study Group (IHSG) as an episode leading to unconsciousness or requiring assistance by a third person.[16] Only clinically important hypoglycemia (Level 2 hypoglycemia, a glucose level of <54 mg/dL with typical hypoglycemic symptoms) was collected. The awareness of this condition by receiving annual injection sites checked from their healthcare professionals and performing self-monitoring of injection site was inquired. Unexplained hypoglycemia was defined as the occurrence of hypoglycemia not related to a mismatch of meal and activities. Lack of insulin rotation was defined as injecting insulin in the same area or less than a fingerbreadth space between injections. Reused insulin needle was defined as using a needle more than 2-times. The frequency of reused needle was further classified as 3-times/needle, 4–5-times/needle, and more than 5-times/needle. Patients who use insulin less than 6 months, follow-up at our diabetes center less than 3-times in the past 12 months, and those who declined participation were excluded from the study.

Patients also underwent a careful clinical examination of the injection site by well-trained nurses. A training workshop for all six experienced diabetes nurse educators to standardize the detection method of lipodystrophy had been conducted by a senior nurse educator who had been working for more than 25 years as a diabetes nurse educator. Experienced diabetes nurse educators, skilled in performing observation and palpation techniques, evaluated the presence of LH or LA in all patients. The inspection of injection site was done carefully with using direct and tangential light and then a gentle palpation technique involving fingertip movements followed by pinching maneuver in the suspected LH area. A clinical grading of LH was applied (Grade 1: lipohypertrophy without visible skin lesion but increased palpable density of subcutaneous tissue; Grade 2: severe hypertrophy with increased density of the injection site).[8] Lipoatrophy at any injection site was noted separately. Clinical parameters including the most recent glycated hemoglobin (A1C) value in the previous 3 months, were all recorded and analyzed. Ultrasonographic studies were performed by an experienced radiologist in some patients with equivocal area of LH or some patients who had concurrent LH and LA. If ultrasound findings suggest other subcutaneous lesions (such as lipoma, hematoma, cyst, etc.), the participant will be excluded from the study. All procedures followed were in accordance with the Declaration of Helsinki. All participants provided

Table 1 Demographic Data of Studied Participants (N=400)

	Total (N=400)	T1DM (N=56)	T2DM (N=344)
Age	65.6±15.4	45.2±13.7	68.9±12.9
Female	53.5%	48.2%	54.4%
Education			
-Less than high school	156 (39.0%)	2 (3.6%)	154 (44.8%)
-High school	86 (21.5%)	9 (16.1%)	77 (22.4%)
-Bachelor degree or colledge	116 (29.0%)	32 (57.1%)	84 (24.4%)
-Higher than bachelor degree	42 (10.5%)	13 (23.2%)	29 (8.4%)
Duration of DM	23.0±10.2	20.1±11.6	23.5±9.8
Duration of insulin (years)	11.4±8.7	18.9±11.0	10.2±7.6
BMI (kg/m^2)	26.2±4.8	23.8±3.6	26.5±4.8
A1C (%NGSP)	7.9±1.6	7.8±1.5	7.9±1.6
Daily insulin dose (units/day)	41.9±24.9	46.5±17.8	41.1±25.8
Daily insulin dose (unit/kg/day)	0.6±0.3	0.7±0.3	0.6±0.3
Type of insulin*			
Human insulin	150 (27.9%)	16 (24.6%)	134 (36.8%)
-Regular insulin	21	8	13
-NPH	15	4	11
-Pre-mixed human insulin	114	4	110
Insulin analog	387 (72.1%)	49 (75.4%)	230 (63.2%)
-Aspart	81	19	62
-Lispro	84	25	59
-Glulisine	18	4	14
-Glargine U100	96	19	77
-Glargine U300	31	5	26
-Detemir	9	2	7
-Degludec	68	17	51
Insulin device			
-Insulin pen	375 (93.8%)	48 (85.7%)	327 (95.0%)
-Insulin syringe	20 (5.0%)	6 (10.7%)	14 (4.1%)
-Mixed (pen and syringe)	5 (1.2%)	2 (3.6%)	3 (0.9%)
Patients with concurrent anti-diabetic medications (%)	218 (54.5%)	11 (19.6%)	207 (60.2%)
Specified type of anti-diabetic medications#			
-Sulfonylurea	28	0	28
-Metformin	162	5	157
-DPP4 inhibitor	82	3	79
-Thiazolidinedione	58	2	56
-SGLT2 inhibitor	48	4	44
-GLP1 receptor agonist	12	0	12

Notes: *The denominator was 537, due to some patients using more than one type of insulin. #Some patients received more than one type of anti-diabetic medication.

informed consent and the Ethics Committee of Theptarin Hospital approved the study (EC 09/2018). Any data intended for sharing were de-identified.

Statistical Analysis

Based on a previous meta-analysis which demonstrated the prevalence of LH at 38%,[7] this study would require a sample

size of 361 subjects for estimating the expected proportion with 5% absolute precision and 95% confidence.[17] All statistical analyses were conducted using the Statistical Package for the Social Sciences (version 22.0; SPSS, Armonk, NY, USA). Data is presented as mean±standard deviation (SD) when Gaussian distribution of the continuous data was observed, and as median (Interquartile range, IQR) when the distribution was not normal. The categorical data are presented as percentages. Descriptive statistics for the categorical variables were assessed using the χ^2 and for the continuous variables using Student's *T*-test, paired and unpaired, or the Mann Whitney *U*-test and Wilcoxon signed-ranks test when applicable. Variables with established association with insulin-induced lipohypertrophy were selected for univariate logistic regression analysis, and those with a *P*-value<0.05 were included in the multivariate models with forward variable selection to determine associated clinical factors and the presence of lipohypertrophy. Results are expressed as odds ratios (ORs) with their 95% confidence intervals (CI). The frequency of unexplained hypoglycemia was also compared between patients with and without LH. *P*-value<0.05 was considered statistically significant. The study was registered retrospectively with www.clinicaltrials.in.th (TCTR20190707003), registered 6 July 2019.

Results

Baseline Demographic and Clinical Characteristics

A total of 400 patients were recruited into the study (female=53.5%, T2DM=86%, mean age=65.6±15.4 years,

Table 2 The Details of Insulin Regimens and Injection Techniques in Studied Participants

	Total (N=400)	T1DM (N=56)	T2DM (N=344)
Insulin regimen			
• Mixed split	155 (38.8%)	7 (12.5%)	148 (43.0%)
• Basal bolus	87 (21.8%)	43 (76.8%)	44 (12.8%)
• Basal plus	60 (15.0%)	5 (8.9%)	55 (16.0%)
• Basal only	86 (21.4%)	–	86 (25.0%)
• Others	12 (3.0%)	1 (1.8%)	11 (3.2%)
Location of injection site			
• Abdomen	371 (92.8%)	43 (76.8%)	328 (95.3%)
• Thigh	4 (1.0%)	–	4 (1.2%)
• Arm	1 (0.2%)	1 (1.8%)	–
• Mixed	23 (5.8%)	11 (19.6%)	12(3.5%)
• Hip	1 (0.2%)	1 (1.8%)	–
Rotation injection site			
• Yes	298 (74.5%)	41 (73.2%)	257 (74.7%)
• No	102 (25.5%)	15 (26.8%)	87 (25.3%)
Needle length			
• 4 mm	20 (5.0%)	2 (3.6%)	18(5.2%)
• 5 mm	82 (20.5%)	13 (23.2%)	69 (20.1%)
• 6 mm	200 (50.0%)	27 (48.2%)	173 (50.3%)
• 8 mm	93 (23.2%)	11 (19.6%)	82 (23.8%)
• Others	5 (1.3%)	3 (5.4%)	2 (0.6%)
Reused insulin needles			
• Yes	378 (94.5%)	53 (94.6%)	325 (94.5%)
3 times	88 (23.3%)	13 (24.5%)	75 (23.1%)
4–5 times	87 (23.0%)	10 (18.9%)	77 (23.7%)
>5 times	203 (53.7%)	30 (56.6%)	173 (53.2%)
• No	22 (5.5%)	3 (5.4%)	19 (5.5%)

duration of diabetes=23.0±10.2 years, median of insulin treatment=10 (IQR=4–16), years, usage of insulin analog=72.1%, A1C=7.9±1.6%) were studied. Only 28.5% of all participants had optimal glycemic control (A1C<7.0%). The demographic and clinical characteristics of the participants are presented in Table 1. The details of insulin regimens and injection techniques are presented in Table 2. In people with T2DM, human premixed insulin was the most commonly used insulin (43.0%). Only 12.8% of T2DM participants received a basal-bolus insulin regimen. Syringes were used only in 6.2% of all participants. Needles with a 6 mm length were most commonly used (50.0%), followed by 8 mm (23.3%), and 5 mm (20.5%). The abdomen was the most frequent site of injection (92.8%). Most of the study subjects (74.5%) rotated the insulin injection sites. Reuse of needles was very common (94.5%), with the majority reusing a needle more than 5-times. In the past 3 months, severe hypoglycemia was found in only three patients (0.8%), two of whom had T1DM. Mismatch between insulin and meal caused severe hypoglycemia in all patients. Clinically important hypoglycemia (level 2 hypoglycemia) was found in 10 patients (2.5%), with fiveof these patients having the definition of unexplained hypoglycemia in our present study. The frequency of unexplained hypoglycemia had been reported 1–2-times over the previous 3 months in 80% of patients and 3–6-times over the previous 3 months in 20% of patients.

The Prevalence and Associated Risk Factors of Insulin-Induced Lipohypertrophy

The overall prevalence of insulin-induced LH was 37.2% (T1DM=46.4% and T2DM=35.5%) with grade 2 (severe LH) in 45.9% of all patients with LH, as shown in Figure 1. Compared to patients without LH, those with LH had a longer diabetes duration and insulin therapy duration, were treated with higher insulin dose, incorrect rotation of injection sites, and reusing insulin needles (≥2-times) as shown in Table 3. The highest prevalence (57.5%) was observed in long-standing (≥10 years) T1DM patients. Multivariate analysis revealed the duration of insulin use (≥10 years), use of human insulin, and incorrect rotation of injection sites were independently associated with LH, as demonstrated in Table 4. The strongest factor associated with LH was incorrect rotation of injection sites (OR=26.14; 95% CI=13.68–49.95). The incidence of unexplained hypoglycemia in the past 3 months was reported in 1.3% of all participants. The patients with LH were found to increase the risk of unexplained hypoglycemia by 7-times when compared with patients without LH (2.7% vs 0.4%, *P*-value=0.045)

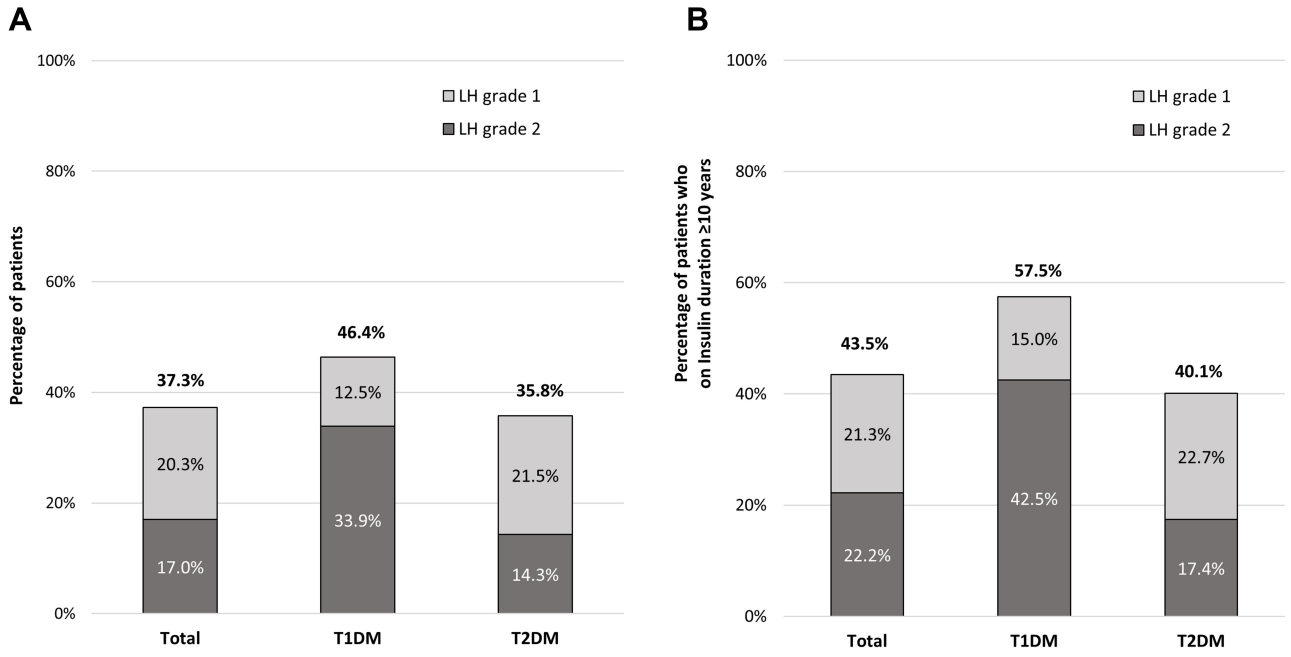

Figure 1 (**A**) The overall prevalence of insulin-induced lipohypertrophy and prevalence stratified by type of diabetes and duration of insulin treatment. (**B**) The prevalence of insulin-induced lipohypertrophy in people with long-standing (≥10 years) DM and prevalence stratified by type of diabetes.

Table 3 Comparison of Clinical Parameters and Glycemic Control in Patients with and without Insulin-Induced Lipohypertrophy

	Patients with LH (N=149)	**Patients without LH (N=251)**	***P*-value**
Age	64.8±14.2	66.0±16.1	0.420
Female	71 (47.7%)	143 (57.0%)	0.071
Education			0.338
• Less than high school	55 (37.2%)	101 (40.1%)	
• High school	31 (20.9%)	55 (21.8%)	
• Bachelor degree or colledge	50 (33.8%)	66 (26.2%)	
• Higher than bachelor degree	12 (8.1%)	30 (11.9%)	
Durationof DM	24.1 ± 8.9	22.4 ± 10.8	0.103
Duration of insulin (years)	13.4 ± 9.2	10.3 ± 8.1	0.001
BMI (kg/m^2)	25.9 ± 4.8	26.3 ± 4.8	0.437
A1C (%NGSP)	7.8 ± 1.5	7.9 ± 1.7	0.545
Daily insulin dose (units/day)	43 ± 24	41 ± 25	0.439
Daily insulin dose (unit/kg/day)	0.6 ± 0.3	0.6 ± 0.3	0.441
Type of insulin			0.021
• Human insulin	54 (36.2%)	59 (23.5%)	
• Insulin analog	88 (59.1%)	181 (72.1%)	
• Both types of insulin	7 (4.7%)	11 (4.4%)	
Insulin device			0.265
• Insulin pen	136 (91.3%)	239 (95.2%)	
• Insulin syringe	10 (6.7%)	10 (4.0%)	
• Mixed	3 (2.0%)	2 (0.8%)	
Insulin regimen			0.074
• Mixed split	61 (41.2%)	94 (37.3%)	
• Basal bolus	27 (18.2%)	60 (23.8%)	
• Basal plus	29 (19.6%)	31 (12.3%)	
• Basal only	29 (19.6%)	57 (22.6%)	
• Others	2 (1.4%)	10 (4.0%)	
Location of injection site			0.282
• Abdomen	143 (96.0%)	228 (90.8%)	
• Thigh	-	4 (1.6%)	
• Arm	-	1 (0.4%)	
• Mixed	6 (4.0%)	17 (6.8%)	
• Hip	-	1 (0.4%)	
Rotation injection site			<0.001
• Yes	60 (40.3%)	238 (94.8%)	
• No	88 (59.7%)	13 (5.2%)	
Needle length			0.652
• 4 mm	5 (3.4%)	15 (6.0%)	
• 5 mm	30 (20.1%)	52 (20.7%)	
• 6 mm	75 (50.3%)	125 (49.8%)	
• 8 mm	38 (25.5%)	55 (21.9%)	
• Others	1 (0.7%)	4 (1.6%)	
Reused insulin needles			0.057
• Yes	145 (97.3%)	233 (92.8%)	
• No	4 (2.7%)	18 (7.2%)	

Table 4 Factors Associated with the Presence of Insulin-Induced Lipohypertrophy

Variables	Univariate			Multivariate		
	OR	P-value	95% CI	OR	P-value	95% CI
T1DM	1.58	0.117	0.89–2.79			
Female	0.67	0.057	0.45–1.01			
Education less than high school	0.88	0.564	0.58–1.34			
BMI <25 kg/m^2	1.24	0.293	0.83–1.87			
Duration of insulin ≥10 years	1.79	0.006	1.19–2.70	1.83	0.025	1.08–3.09
Number of daily insulin injection	0.98	0.936	0.64–1.52			
Use of human insulin	1.82	0.006	1.19–2.80	1.78	0.037	1.04–3.05
Insulin dose ≥0.6 units/kg/day	1.03	0.872	0.69–1.55			
Incorrect insulin rotation	24.93	<0.001	13.27–46.86	26.14	<0.001	13.68–49.95
Use of needle length ≥8 mm	1.17	0.510	0.733–1.87			
Reuse insulin needles	2.769	0.070	0.92–8.35			
3 times	2.972	0.067	0.93–9.52			
4–5 times	2.491	0.126	0.77–8.02			
>5 times	2.808	0.071	0.92–8.60			

The Prevalence and Clinical Characteristics of Insulin-Induced Lipoatrophy

A total of four cases (male=50%, mean age=60.5±17.1 years, duration of diabetes=27.0±11.4 years, median of insulin treatment=16 years, A1C=8.5±1.1%, median total daily dose of insulin=40 units per day) of insulin-induced LA were found, which accounted for only 1.0% of all participants. Three patients had T2DM and one patient had T1DM. All LA cases had a concurrence palpable area of lipohypertrophy. Lipoatrophic areas were developed in the abdominal area, both on the same side and the opposite side of lipohypertrophic areas. Ultrasonographic findings of lipoatrophy revealed a focal area of decreased thickness and increased heterogeneous echogenicity of subcutaneous fat texture, as demonstrated in Figure 2. One patient had suspected insulin-derived localized amyloidosis based on palpable subcutaneous mass at sub-umbilical region and homogeneous hypoechoic fat interspersed with hyperechoic linear echogenic area. However, the patient refused to have excision for confirmed diagnosis.

All LA patients, except for one, used various recombinant insulin analogs. Repeated insulin injections at the same sites were reported in all patients, and unexplained hypoglycemia was found in 80% of the patients. None of the patients received their injection sites checked at least annually from their healthcare professionals.

Awareness of Insulin-Induced Lipodystrophy

As revealed in Figure 3, only about 30% of patients had their injection sites checked at least annually by their healthcare professionals and more than half of the patients had received no injection checking in the last 1 year. Almost two-thirds of all participants never performed self-monitoring of the presence of insulin-induced lipodystrophy.

Discussion

Our present study confirms previous findings from a recent meta-analysis that the prevalence of lipohypertrophy was a common complication in insulin-treated people with diabetes and was associated with an increased risk of unexplained hypoglycemia. Unfortunately, it received little attention from healthcare professionals, and many patients still have inadequate instructions on insulin injection

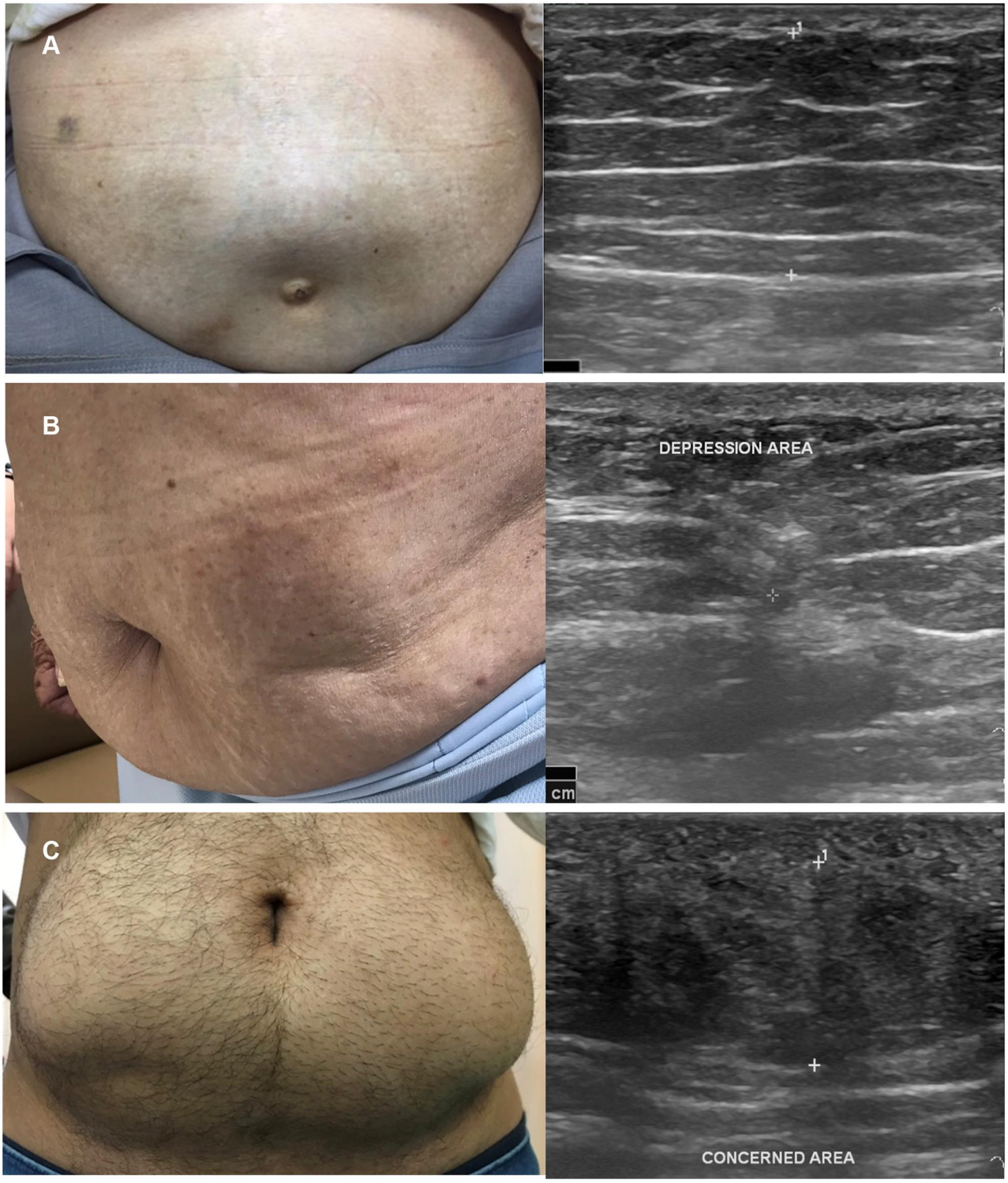

Figure 2 (**A**) A typical insulin-induced lipohypertrophy in T2DM patient with ultrasound characteristics of thickening heterogeneous echogenicity of subcutaneous fat. (**B**) Insulin-induced lipoatrophy in a patient with long-standing T2DM with ultrasonographic findings of lipoatrophy revealed a focal area of decreased thickness and increased heterogeneous echogenicity of subcutaneous fat texture. (**C**) A T1DM patient with suspected insulin-derived localized amyloidosis based on palpable subcutaneous mass at subumbilical region and homogeneous hypoechoic fat interspersed from ultrasound.

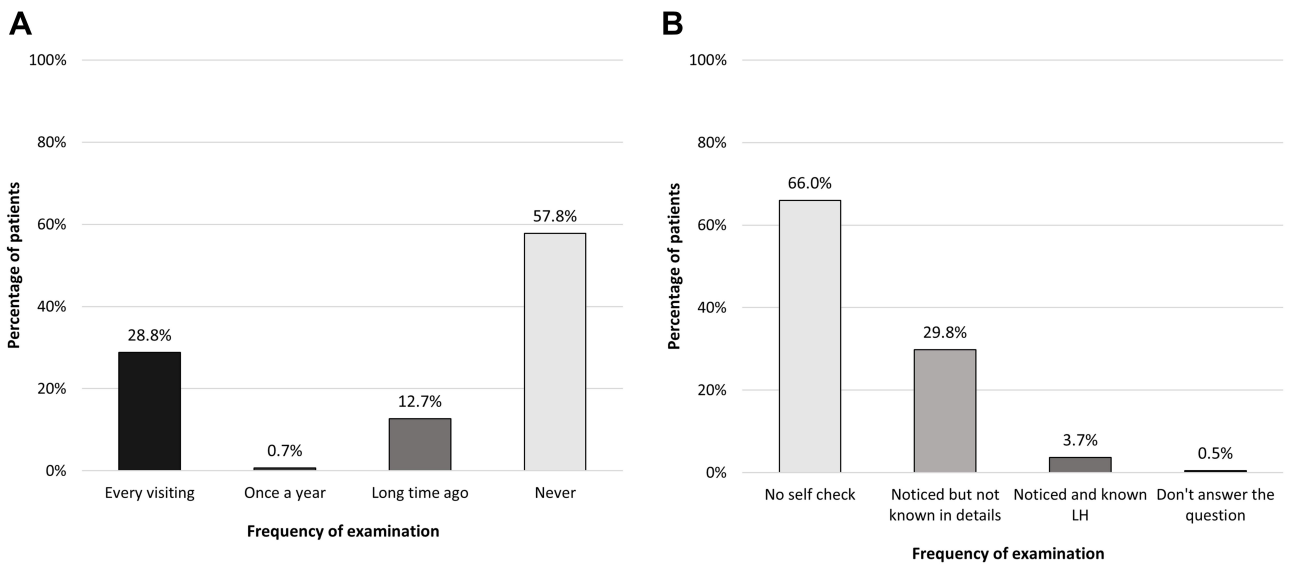

Figure 3 (**A**) Frequency of lipodystrophy checking from healthcare professions. (**B**) Self-checking the presence of lipodystrophy by patients.

technique. Poor injection technique, especially incorrect rotation of insulin injection sites, leads to the occurrence of LH in our study. Since the advent of recombinant human insulin and insulin analogs, insulin-induced lipoatrophy, which is believed to be related with immune complex-mediated inflammatory reaction, is rarely seen today.[18] Interestingly, concurrent occurrence of lipoatrophy and lipohypertrophy in the same patient had been found up to 1.0% in our series.

Subcutaneous adipose tissue has been known to be a local target of exogeneous insulin action since 1950.[19] The lipodystrophic reactions from insulin could roughly be divided into hypertrophic or atrophic lesions. While LH is most commonly seen in those with poor injection technique since the discovery of insulin, LA was commonly found before the 1970s when impure animal insulin was used. With the availability of recombinant insulin, the prevalence of LA was reported at only 0.2–1.4%.[12] These skin complications occurring at insulin injection sites not only cause cosmetic concerns but also are known to cause impaired absorption of insulin. In a recent combined glucose-clamp/meal test study to quantify the impact of insulin lispro injection into LH area,[20] the researchers found that the LH area injection increased the variability of both insulin absorption and insulin action in euglycemic clamps. As a result, postprandial hyperglycemia (≥26% higher in plasma glucose concentrations) was observed in people with T1DM with LH area injection. Therefore, it should be emphasized that suboptimal glycemic control and in patients with unexplained hypoglycemia, treating physicians should inspect and examine the presence of LH.[21]

Repeated trauma to the same injection site when patients fail to rotate injections and/or repeated use of the same needle was reported worldwide.[5] The patient usually finds less painful injection when injected into LH area, and this could further aggravate the enlargement of LH area. In the extreme cases, insulin-derived localized amyloidosis or "insulin ball" could develop, and cosmetic surgery is required to manage this cutaneous complication.[22–24] In our series, one case of suspected insulin-derived amyloidosis in a patient with long-standing T1DM who repeated injected insulin glargine and insulin aspart into the same abdominal area over 15 years was found. The patient denied further investigations with abdominal computed tomography (CT) and excision. In vitro studies reported that toxicity of insulin amyloid fibrils cause fat necrosis in the surrounding tissue, and recombinant insulin or human insulin could lead to this uncommon problem.[25] Therefore, the role of imaging including ultrasound and CT scan could differentiate insulin-derived localized amyloidosis from the more common insulin-induced LH.

Consistent to other cross-sectional studies from Caucasian patients,[2,8] we also found that the prevalence of LH was more common in people with T1DM, especially in long-standing T1DM patients. However, a milder form of LH (or LH grade 1) was detected more frequently

in people with T2DM. Specific training in inspection and palpation techniques should be emphasized to healthcare professionals to identify smaller and flatter LH area.[26] Sometimes, ultrasound scans are needed in equivocal lesions to identify culprit lesions in an early phase.[27] Ideally, treating physicians should perform a thorough injection sites inspection in all insulin-treated patients in every visit. However, time constraint is one of the barriers physicians face in a routine diabetes clinic. Therefore, focusing on higher risk patients (such as people with T1DM, all patients with duration of insulin use ≥10 years, patients who reusing insulin needles ≥3 times, etc.) would help busy physicians to triage the higher risk patients. Moreover, training diabetes nurse educators would also facilitate screening and educating patients in the primary care setting.[28]

Apart from poor injection techniques, insulin devices and needles might also play a role in the development of LH from the possible greater tissue injury from mismatch devices and repetitive uses.[6] Theoretically, needle lengths should be as short as possible to minimize tissue trauma and to avoid inadvertent intramuscular administration, especially in skinny people.[29] Most insulin pen needles range from 4–12 mm in length and 29–32 gauge in diameter. Based on the results of our study, which was conducted in the private setting, the majority of patients used insulin pens, with half of them using a 6-mm needle length. However, if it is possible, the smallest 4 mm needles would carry the least risk of tissue trauma and avoid intramuscular injection.[30] Regarding reusing insulin needles (≥2-times), the results revealed that it was a very common practice in our participants. Possible explanations could be economic reasons or convenience for patients. Even though our present study revealed no association between reuse of insulin needle and the occurrence of LH, patients should be educated to not reuse needles if and needle tip deformity or increased pain were observed.[31,32] Moreover, the dose of insulin which needed to be consumed more in LH patients might outweigh the economic concern for reused needles.[33]

Another spectrum of insulin-induced lipodystrophy is insulin-induced lipoatrophy which the prevalence decreased sharply from 10–55% of patients using animal-derived insulin to less than 2% in the present day.[12] However, our study was also consistent with previous reports that insulin analogs did not prevent patients from developing this complication and concurrence of LH and LA in the same patient could be seen.[13,14] Recognizing this rare insulin reaction and timely detection of lipoatrophy with ultrasound as a non-invasive simple imaging modality is necessary to avoid further injection in the skin lesion. Even though specific treatment of LA is still unavailable, therapeutic trials of dexamethasone and cromolyn sodium had been reported successfully in the anecdotal cases.[34,35]

This study has several limitations that should be acknowledged. First, this was a cross-sectional study from a private tertiary diabetes center in Bangkok. The results may not be applicable to other populations. Further multi-center studies are required to confirm these findings. Second, it was not possible to use ultrasound which is the gold standard to detect lipodystrophy in all participants in this study so the prevalence of lipodystrophy could be underestimated. However, all experienced diabetes nurse educators who conducted this study had been trained to minimize inter-observer variation in observation and palpation techniques. Moreover, the clinical significance of "subclinical lipohypertrophy", which was identified by ultrasonographic features of hyperechogenicity in non-palpable injection area, remains unknown. Third, the objective data of documented hypoglycemic episodes and responses after avoiding injection into LH area could not be examined. Nevertheless, this study is represented by the relatively large sample size with a comprehensive set of risk factors assessment. To the best of our knowledge, this study is also the first study in a Southeast Asian population. Future prospective studies should be conducted to improve insulin injection techniques among LH patients and determine whether effects of interventions to the impact of glycemic control and risk of hypoglycemia.[36]

Conclusion

Insulin-induced lipodystrophy is still an overlooked complication in the modern era of diabetes care. While the presence of lipohypertrophy is very common and significantly associated with the occurrence of erratic glucose control and unexplained hypoglycemia, the presence of lipoatrophy is rare but is still seen in some exceptional patients. Insulin injection technique continues to be suboptimal in many insulin-treated patients, and our study also highlights the need for improved awareness of physicians to recognize these insulin-related skin complications.

Abbreviations

A1C, glycated hemoglobin value; LA, Lipoatrophy; LH, Lipohypertrophy; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus.

Data Sharing Statement

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors declare that they have no competing interests.

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