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REVIEW

The Distinct Ultrasound Characteristics and Prognostic Features of Insulin-Induced Lipohypertrophy: A Systematic Review

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Background: Insulin-induced lipohypertrophy (LH) is a common complication of insulin therapy. However, its ultrasound characteristics, classification, and progression patterns remain poorly understood. This review aimed to systematically analyze the ultrasound characteristics and progression patterns of LH, and explore the relationship between different LH types and clinical outcomes.
Methods: A systematic literature search was conducted from January 2000 to October 2024 in PubMed, Web of Science, Embase, and Cochrane Library following PRISMA guidelines. Studies that examined LH using ultrasound in diabetic patients receiving insulin therapy were included. Two independent reviewers performed study selection and quality assessment using standardized tools.
Results: Twenty studies involving 5067 patients were included. Ultrasound showed significantly higher detection rates (57.6–100%) than physical examination (27.9–79.7%), with subclinical LH reported in 13.0–55% of cases. Twelve studies provided detailed ultrasound characteristics, with most describing well-defined borders, echo patterns predominantly showed hyper-echogenicity, and noted reduced or absent blood flow. Two ultrasound patterns were identified based on nodule size and echo patterns. Follow-up studies demonstrated distinct progression patterns and varying metabolic improvements among different LH types.
Conclusion: Ultrasound reveals three distinct patterns (nodular, diffuse, and hypoechoic), each with unique prognostic features, providing a basis for individualized management.
Keywords: insulin-induced lipohypertrophy, ultrasound, diabetes mellitus, progression, insulin injection, subcutaneous complications

Introduction

Insulin-induced lipohypertrophy (LH) is a common complication characterized by excessive proliferation and hypertrophy of adipocytes at injection sites due to the stimulation of local adipose tissue by insulin.[1] The International Diabetes Federation (IDF) estimates that the number of diabetic patients worldwide will reach More than 1.3 billion by 2050,[2] and a large proportion of them will require insulin therapy, which makes the prevention and treatment of LH even more important. LH not only affects insulin absorption and action, leading to poor glycemic control and increased risk of hypoglycemia,[3,4] but also significantly increases medical costs. Studies have shown that patients with LH require an average of 11 more units of insulin daily compared to those without LH, potentially resulting in an additional 2 billion RMB in annual medical expenditure in China.[5]

Recent meta-analyses indicate that the average prevalence of LH is 30.8%-73.4%.[6,7] These figures may still underestimate the true prevalence due to potential missed diagnoses through traditional visual inspection and palpation. With the application of imaging technologies such as ultrasound, LH detection rates have significantly improved.[8] Ultrasound examination can identify over 40% of lesions missed by clinical examination and provide more objective assessment.[9]

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Studies have shown that LH presents with three distinct sonographic patterns under ultrasound: nodular hyperechoic (65.5%), diffuse hyperechoic (27.5%), and hypoechoic (7.0%).[10] This classification may be associated with LH progression stages and prognosis, but systematic analysis is currently lacking. Accurate identification and classification of ultrasound characteristics of LH have significant clinical implications beyond glycemic control. LH presents multiple challenges including aesthetic problems (such as visible skin deformities and discoloration), physical discomfort, psychological distress, and potential infection risks. Different types of LH may represent different stages of the lesion, affecting not only the degree of insulin absorption but also the severity of these complications. Additionally, the lack of standardized classification hampers proper assessment of these problems and their progression. Although previous studies have documented various complications of LH, the relationship between different ultrasound-detected LH patterns and their associated complications remains poorly understood. Establishing a standardized ultrasound classification system helps in early detection and intervention of LH, providing guidance for comprehensive clinical decision-making including both metabolic management and complication prevention.

Despite the widespread application of ultrasound in LH detection, the lack of standardized diagnostic criteria poses significant challenges in clinical practice. Current ultrasound assessment largely relies on qualitative descriptions rather than standardized quantitative measurements, leading to considerable heterogeneity in reporting and interpreting findings across studies.[8] Various classification systems have been proposed, ranging from simple binary assessments to complex grading schemes,[10,11] but no consensus has been reached on optimal diagnostic standards. This lack of standardization not only hampers the comparison of research findings but also affects clinical decision-making in determining LH severity and appropriate therapeutic adjustments. Therefore, a systematic analysis of ultrasound characteristics and classification of LH is essential for establishing evidence-based diagnostic criteria and improving patient care.

Although clinical observations suggest that LH is reversible, the natural course and time to regression of different types of LH vary significantly. This discrepancy may be related to a variety of factors, including duration of insulin use, injection technique, and individual patient characteristics.[12] However, the importance of these influencing factors has not been fully validated due to the lack of prospective studies with large samples. In current clinical management of existing LH, patients are currently mainly advised to avoid injecting insulin at the lesion site.[7] However, this management strategy presents two key challenges: first, as injection sites decrease, the injection area available to the patient gradually shrink, which may lead to the development of new LH; second, the natural progression and long-term prognosis of established LH remain unclear, complicating clinical decision-making. In-depth study of LH prognosis has important implications: first, understanding the natural course and progression patterns of LH can help to formulate a reasonable follow-up plan and assessment criteria; second, identifying key factors affecting LH prognosis provides a basis for optimizing prevention strategies; third, prognostic studies can evaluate the long-term effects of different interventions, guiding individualized treatment plans.

Current studies on LH primarily focuses on prevalence, risk factors, and diagnostic methods, with relatively insufficient attention to its dynamic evolution process and progression characteristics.[13] Existing reviews are often limited to specific aspects, such as diagnostic techniques[14] or prevention strategies,[15] lacking systematic analysis of the entire LH process. Furthermore, while multiple studies have explored the effects of different interventions, unified treatment protocols and follow-up strategies have not been established.[7,16]

Given these considerations, this study aims to comprehensively analyze the diagnostic characteristics, progression patterns, and outcomes of LH through a systematic literature review for the first time. Special attention is paid to: (1) the diagnostic value of different examination methods; (2) the proposal of an ultrasound-based classification system; (3) exploration of LH progression patterns based on ultrasound findings; (4) outcome characteristics of different types of LH. By integrating existing evidence, this study provides references for clinical practice and directions for future research.

Methods

This systematic review was conducted following standard systematic review methodology. The study protocol was developed in accordance with the PRISMA (2020 statement) guidelines[17] and was registered with PROSPERO (CRD42024603916). To comprehensively evaluate both the diagnostic and prognostic aspects of LH, a dual-track design was adopted. This approach was necessary due to the distinct nature of available evidence - while numerous observational studies have focused on LH detection and characterization (Part A), evidence regarding LH progression is relatively limited and largely based on case reports and small cohort studies (Part B).

Search Strategy

A comprehensive systematic search was conducted in PubMed, Web of Science, Embase, and Cochrane Library from January 2000 to October 2024. The search strategy was developed in consultation with a medical librarian using Medical Subject Headings (MeSH) terms and free-text terms including "insulin", "lipohypertrophy", "ultrasound", "progression", "outcomes", and "follow-up" (detailed search strategy see Appendix 1). Reference lists of included studies and relevant reviews were manually searched to identify additional articles.

Eligibility Criteria

For Part A, studies were eligible if they: (1) were cross-sectional studies, cohort studies, case-control studies, or randomized controlled trials; (2) included diabetic patients receiving insulin therapy; (3) reported LH detection rates or ultrasound characteristics; and (4) were original research with full text published between January 2000 and October 2024.

For Part B, inclusion criteria were: (1) prospective cohort studies, randomized controlled trials, or case reports; (2) diabetic patients diagnosed with LH; (3) reported progression characteristics or metabolic improvements; and (4) original research with full text published during the same period. Conference abstracts, reviews, editorials, duplicate publications, and studies with incomplete data reporting were excluded.

Study Selection and Data Extraction

HY Yang and LL Zhang independently screened titles/abstracts and full texts according to the inclusion/exclusion criteria. Disagreements were resolved through discussion or consultation with HL Liu. For Part A studies, we extracted data on study characteristics (first author, publication year, study design, country/region, population, sample size), patient characteristics (age, duration of diabetes, insulin method, duration of insulin therapy, total daily insulin dose,), LH detection results (LH detection methods, rates by physical examination and ultrasound, agreement between methods, subclinical LH rates), and ultrasound characteristics (morphological features, echo patterns, tissue changes, vascularity, classification systems).

For Part B studies, data extraction included study characteristics (first author, publication year, study design, country/region, sample size, follow-up duration), baseline LH features (LH area, detection rates, distributional characteristics), and progression characteristics (time to changes, changes in different LH types, metabolic improvements).

Quality Assessment

HY Yang and LL Zhang independently assessed the methodological quality of the included studies. The Newcastle-Ottawa Scale was used for observational studies (maximum score 9 points), with studies scoring ≥7 considered high quality, 4–6 as moderate quality, and ≤3 as low quality. Case reports were evaluated using the JBI Critical Appraisal Checklist (10 items), while interventional studies were assessed using either the JBI Critical Appraisal Checklist for Quasi-Experimental Studies or the Revised Cochrane Risk-of-Bias Tool (RoB 2.0) for randomized trials. Disagreements were resolved through discussion or consultation with a third reviewer. Studies rated as low quality (≤3 on the Newcastle-Ottawa Scale, or ≤50% on the JBI Checklist, or high risk on RoB 2.0) were excluded from the review.

Results

Study Characteristics

As demonstrated in Table 1, a total of 20 studies published between 2017 and 2024 were included in this systematic review, comprising 14 observational studies, 3 case reports, 2 interventional studies, and 1 randomized controlled trial. This comprehensive analysis revealed several key advantages: first, ultrasound examination demonstrated significantly higher detection rates (57.6–100%) compared to physical examination (27.9–79.7%); second, the current study review

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Table 1 Included Study Characteristics for Insulin-Induced Lipohypertrophy

First Author (Year)	Country	Study Design	Population	Sample Size	Age (Years)	Diabetes Mellitus Duration (Years)	Insulin therapy	Insulin Duration (years)	Total Daily Insulin (IU)	Detection Methods
Arora (2021)[18]	India	Cross-sectional study	T1DM +T2DM	500	45.2±16.5	11±7	Pen (57.2%); Syringe (42.8%)	8±6	54.9±8.2	PE+US
Gentile (2020)[19]	Italy	Cross-sectional study	T2DM	1247	61±16	11±7	Pen (100%)	8±4	32.70±15.30	PE+US
Volkova (2019)[20]	Russia	Cross-sectional study	T1DM +T2DM	140	45.19±16.34	13.21±8.07	Pen; Syringe	10.02±8.79	34.70±15.62	PE+US
Singha (2021)[21]	India	Cross-sectional study	T1DM	95	13.3±4.1	ND	MDI	ND	27.81±14.44	PE+US
Lin (2021)[22]	China	Cross-sectional study	T1DM +T2DM	120	59.21±14.44	ND	Pen (95%); Syringe (5%)	6.56 ±4.26	36.08 ±19.06	PE+US
Kapeluto (2018)[23]	Canada	Cross-sectional study	T1DM +T2DM	103	75±11.8	ND	Pen (98%)	ND	46.3±8.5	PE+US
Barlas (2023)[24]	Turkey	Prospective cohort	T1DM	66	40.6±14.2	ND	MDI; CSII	ND	MDII:51.9 ±19.0 CSII:44.4±12.9	PE+US
Luo (2021)[25]	China	Cross-sectional study	T1DM +T2DM	316	55.49±17.34	12.83(6.59–19.22)	Pen	6.15	32.70±15.30	PE+US
Gentile (2021)[26]	Italy	Cross-sectional study	T2DM	1227	73±8	12±9	Pen	12±5	43±11	PE+US
Bertuzzi (2017)[11]	Italy	Retrospective study	T1DM	40	37±12	22±12	MDI+CSII	ND	32±16	US
Hashem (2021)[1]	UK	Cross-sectional study	T1DM	74	40.6±14.2	18.3±10.9	MDI	ND	49.8±18.1	US
Yu (2022)[9]	China	Cross-sectional study	T1DM +T2DM	382	ND	ND	MDI	ND	ND	PE+US
Korkmaz[27] (2022)	Turkey	Cross-sectional study	T1DM +T2DM	136	52.87 ± 14.93	15.76 ± 9.20	MDI	11.42 ± 8.26	ND	US
Ucieklak[28] (2022)	Poland	Cross-sectional study	T1DM	79	28 (24–30.5)	15.0 (9–20)	CSII	8.5 ± 4.8	ND	PE+US
Yu (2023)[10]	China	Prospective Cohort	T1DM +T2DM	344	57(30,66)	ND	Pen	6.2	47.9±8.2	US
Gentile (2023)[12]	Italy	Case Report	T2DM	1	74	8	MDI	8	113	PE+US

Smith (2017)[29]	UK	Interventional	T1DM +T2DM	75	ND	ND	MDI	ND	71.6 ± 47.0	PE
Misnikova (2017)[30]	Russia	RCT	T1DM +T2DM	120	18–70	ND	MDI	≥1	ND	PE
Ortiz-Roa (2017)[31]	Colombia	Case Report	T2DM	1	46	8	MDI	ND	45	PE+US
Gentile (2018)[32]	Italy	Case Report	T2DM	1	71	ND	MDI	ND	113	PE+US

Abbreviations: T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; PE, Physical Examination; US, Ultrasound examination; MDI, Multiple daily insulin injections; CSII, Continuous subcutaneous insulin infusion; ND, No Data reported; RCT, Randomized controlled trials.

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identified distinct ultrasound characteristics that could help standardize LH classification; and third, the analysis of progression patterns provided new insights into treatment strategies.

Among the included studies, 8 studies included both T1DM and T2DM patients, 5 studies focused exclusively on T1DM, and 2 studies examined T2DM only. The analysis showed that while LH characteristics were similar between T1DM and T2DM patients, some differences were noted in prevalence rates and progression patterns.

The study search and screening process is shown in Figure 1. Among the 14 studies assessed using the Newcastle-Ottawa Scale, 13 (92.9%) were rated as high quality (score ≥7) and 1 (7.1%) as moderate quality (score = 6). All three case reports scored ≥8 on the JBI checklist, indicating good reporting quality. Both interventional studies and the randomized controlled trial demonstrated high methodological quality. Overall, the included studies showed good methodological quality, providing reliable evidence for this review. (Supplementary Table 1)

Part A comprised 15 studies, predominantly cross-sectional studies[1,9,11,18,20–23,25–28] (n=12), along with prospective cohort studies[10,24] (n=2) and a case-control study[19] (n=1). The total sample size was 4,869 patients, with studies including mixed populations[9,10,18,20,22,23,25,27] (T1DM+T2DM; n=8), T1DM only[1,11,21,24,28] (n=5), and T2DM[19,26] only (n=2). Individual study sample sizes ranged from 20 to 1,247 participants, with patient ages spanning from 13 to 75 years. Insulin delivery methods included insulin pens[10,18–20,22,23,25,26] (n=8), multiple daily injections[1,9,21,27] (MDI; n=4), continuous subcutaneous insulin infusion[28] (CSII; n=1), and mixed methods[11,24] (n=2).

Part B included 8 studies: case reports[12,31,32] (n=3), prospective cohort studies[10,20] (n=2), a randomized controlled trial[30] (n=1), retrospective study[11](n=1) and an interventional study[29] (n=1). Sample sizes ranged from single cases to 384 patients, involving both type 1 and type 2 diabetes patients. Studies were conducted in Italy, China, the UK, and Russia, with follow-up periods ranging from 10 days to 12 months.

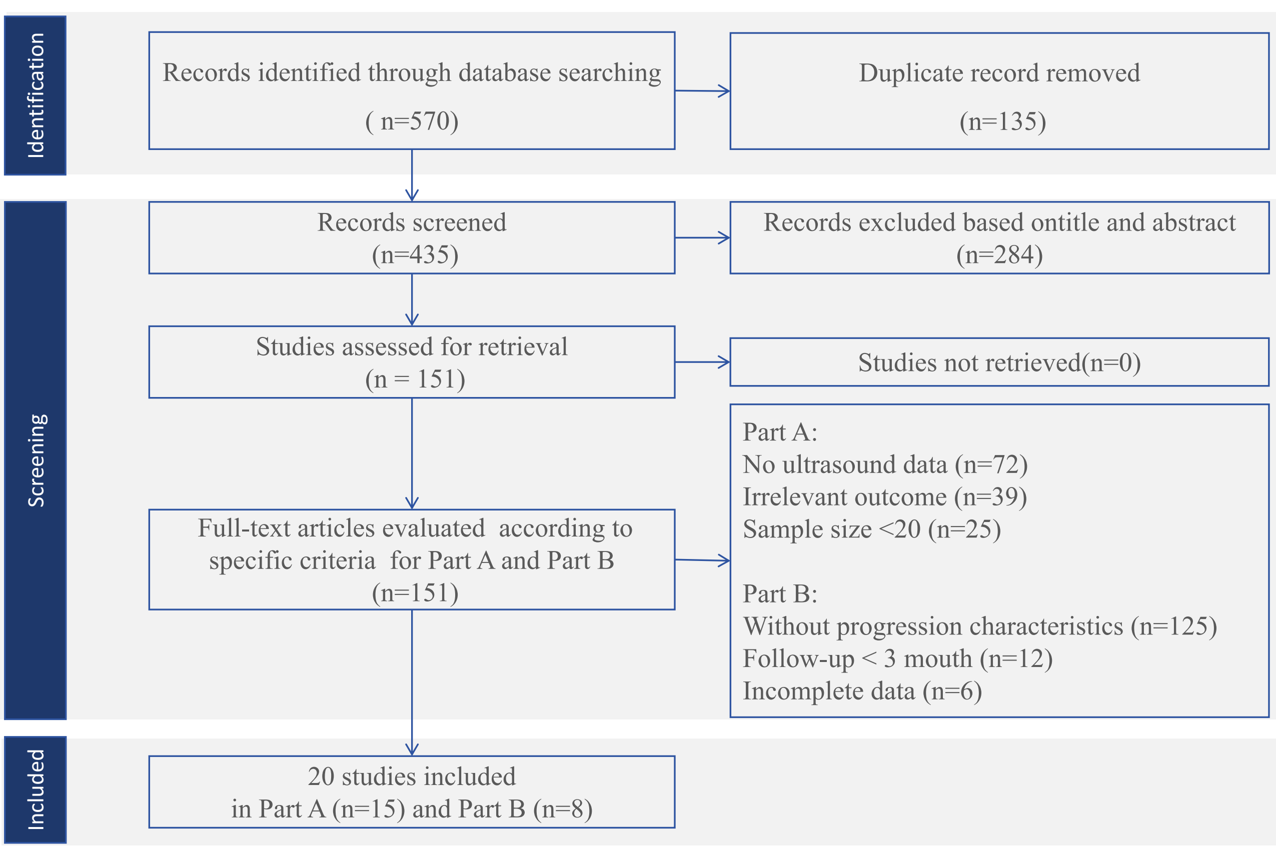

Figure 1 Flowchart on literature inclusion.

Detection Rates and Agreement Analysis

As shown in Table 2, regarding diagnostic methods, 11 studies[9,18–26,28] employed both physical examination and ultrasound, while 4[1,10,11,27] used ultrasound alone. Physical examination detection rates ranged from 27.9% to 79.7% (median 55.3%), while ultrasound detection rates were higher, ranging from 57.6% to 100% (median 82.9%). Subclinical LH rates were reported in 9 studies,[9,18–20,22–25,28] ranging from 13.0% to 55.0%. Only 3 studies[19,23,28] assessed the agreement between the two methods, with κ values ranging from 0.129 to 0.99. High agreement was reported by Gentile (2020)[19] (κ=0.99), while Ucieklak (2022)[28] reported lower agreement (κ=0.129).

Ultrasound Characteristics Analysis

As presented in Table 3, twelve studies[1,10,11,18–25,27] provided detailed ultrasound characteristics of LH. Morphologically, all studies reported lesions located in the subcutaneous fat layer, with most describing well-defined borders (n=8)[10,19,20,22,24,25,27,28] and absence of capsule[10,20,22–24,28] (n=6). The ultrasound findings consistently demonstrated that LH lesions appear as well-circumscribed areas in subcutaneous tissue, with sizes ranging from 1.8mm to over 40mm[1]. Quantitative measurements showed increased tissue thickness in LH areas (13.0±5.7mm) compared to normal tissue (8.22±4.04mm).[18] Echo patterns predominantly showed hyper-echogenicity, presenting as either nodular or diffuse patterns, sometimes with hypoechoic halos. Tissue changes mainly manifested as subcutaneous tissue thickening, connective tissue distortion, and interstitial edema. Of the 9 studies reporting vascularity, all noted reduced or absent blood flow. Two classification systems were proposed: a 0–4 grade system based on nodule size, and a three-type system based on echo patterns.

Progression and Outcomes of Insulin-Induced LH

Based on 8 included studies,[10–12,20,29–32] ultrasound detection rates for LH ranged from 48.8% to 100%. The most common type was nodular hyperechoic (65.5%), followed by diffuse hyperechoic (27.5%), and hypoechoic (7.0%).[10] Follow-up observations showed that nodular hyperechoic LH could completely resolve within 6 months, while diffuse

Table 2 Comparison of Insulin-Induced Lipohypertrophy Detection Rates Between Physical Examination and Ultrasound (Part A)

First Author (Year)	Physical Examination Detection (%)	Ultrasound Detection (%)	Agreement (κ value)	Subclinical LH Rate (%)
Arora (2021)[18]	44.6	58	ND	13.4
Gentile (2020)[19]	44.6	57.6	0.99	13.0
Volkova (2019)[20]	27.9	82.9	ND	55
Singha (2021)[21]	45.2	ND	ND	ND
Lin (2021)[22]	46.6	69.1	ND	22.5
Kapeluto (2018)[23]	55.3	72.8	0.5	24.3
Yu (2023)[10]	ND	74.1	ND	ND
Barlas (2023)[24]	62.1	78.8	ND	16.7
Luo (2021)[25]	65.5	85.4	ND	19.9
Gentile (2021)[26]	59	ND	ND	ND
Bertuzzi (2017)[11]	ND	100	ND	ND
Hashem (2021)[1]	ND	100	ND	ND
Yu (2022)[9]	73.0	87.2	ND	14.2
Korkmaz (2022)[27]	ND	87.5	ND	ND
Ucieklak (2022)[28]	79.7	94.9	0.129	15.3

Abbreviation: ND, No Data reported.

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Table 3 Ultrasound Characteristics of Insulin-Induced Lipohypertrophy

First Author (Year)	Morphological Features	Echo Patterns	Tissue Changes	Vascularity	Classification/Grading
Arora (2021)[18]	Located in subcutaneous layer	Heterogeneous echo areas	Thickened subcutaneous tissue	ND	ND
Gentile (2020)[19]	Located in subcutaneous layer; Well-circumscribed; Variable size;	Hyperechoic; Mixed echogenicity	Distorted connective tissue	ND	ND
Volkova (2019)[20]	Round formations; Well-defined borders; No capsule	Hyperechoic; Homogeneous structure	ND	Avascular	ND
Singha (2021)[21]	Located in subcutaneous layer	Heterogeneous echogenic changes	Deep deflection of muscular band	Diminished vascularity	ND
Lin (2021)[22]	Located in subcutaneous layer; Well-defined borders; No capsule	Nodular hyperechoic; Interstitial hypoechoic	Distorted connective tissue	Almost no blood flow signal	ND
Kapeluto (2018)[23]	Well-circumscribed; No capsule	Hyperechoic foci; Nodular shape with hypoechoic halo	Heterogeneous echotexture; Distorted surrounding connective tissue	Absence of vascularity	ND
Yu (2023)[10]	Located in subcutaneous layer; No capsule	Nodular hyperechoic; Diffuse hyperechoic; Hypoechoic	Interstitial edema around hyperplastic nodules	ND	Nodular hyperechoic LH Diffuse hyperechoic LH Hypoechoic LH
Barlas (2023)[24]	Located in subcutaneous layer; Well-circumscribed; No capsule	Heterogeneous echotexture	Distorted connective tissue	No vascularity	ND
Luo (2021)[25]	Located in subcutaneous layer	Heterogeneous echogenicity	Interstitial edema	ND	ND
Gentile (2021)[26]	ND	ND	ND	ND	ND
Bertuzzi (2017)[11]	Located in subcutaneous layer	Iso-hyperechogenic with fibrotic component; Iso-echogenic with mixed component; Iso-hypoechogenic without fibrotic segments	Deep deflection of the muscular band in correspondence to the subcutaneous thickness	Reduction of the vascular	Type A: Iso-hyperechogenic with predominant fibrotic component Type B: Iso-echogenic with mixed component and fibrotic segments with edema-like islands Type C: Iso-hypoechogenic without fibrotic segments

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Hashem (2021)[1]	Nodules 1.8–40mm; Disrupted dermal layers	Areas of increased reflectivity; Hypoechoic areas (necrotic tissue)	Dermal thickness increase (30–50%)	ND	Grade 0: Normal Grade 1: Diffuse areas without clear nodules Grade 2: Nodules 1–5.9mm Grade 3: Nodules 6–9.9mm Grade 4: Nodules ≥10mm
Yu (2022)[9]	Prominent and/or thickened tissue at injection sites, sometimes resulting in lump formation under the skin	ND	Fibrosis, and adipocyte enlargement and proliferation	Decreased vascularity	ND
Korkmaz (2022)[27]	Located between epidermis and muscle layer; Clear circumscription	Hyperechogenic areas: prevailing fibrotic component; Hypoechogenic areas: edema or fluid components without fibrotic segments	Distortion of surrounding connective tissue	Absence of vascularity	ND
Ucieklak (2022)[28]	Located in subcutaneous layer; Soft benign nodules; Clear circumscription; No capsule	Hyperechogenic foci with defined borders or nodular shape with hypoechogenic halo; Heterogeneous echotexture	Distortion of surrounding connective tissue	Absence of vascularity	ND

Abbreviations: LH, insulin-induced lipohypertrophy; ND, No Data reported.

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hyperechoic type showed partial improvement. Metabolically, after discontinuing injections at LH sites, patients showed mean HbA1c reductions of 0.8–2.2% and daily insulin dose reductions of 5.6–30%. Different LH types showed varying resolution times: nodular hyperechoic type had the best prognosis, while diffuse and hypoechoic types required longer recovery periods, with some cases needing surgical intervention. Study follow-up periods ranged from 10 days to 12 months, with most studies using 6 months as the observation endpoint (see Table 4).

Discussion

This systematic review presents a comprehensive analysis of ultrasound characteristics, classification, and prognostic relationships of insulin-induced LH, and proposes a hypothesis of LH progression based on ultrasound manifestations. Through systematic evaluation of 20 studies, ultrasound examination demonstrated significant advantages over physical

Table 4 Progression and Outcomes of Insulin-Induced Lipohypertrophy (Part B)

First Author (Year)	Baseline LH Features	Ultrasound Changes	Clinical Signs	Metabolic Improvements	Interventions	Follow Up Duration
Gentile (2023)[12]	Two lesions near navel: right 9×8cm, left 8×6cm; hard, hyperpigmented	Fluid collection disappeared; tissue softening	Depigmentation; texture softening	HbA1c decreased by 2.2%; 30% reduction in insulin dose	Proper injection technique; avoid LH areas	12 months
Yu (2023)[10]	255/344 with LH: nodular (65.5%), diffuse (27.5%), hypoechoic (7.0%)	Nodular type resolved; diffuse type shrunk	Palpation improvement	HbA1c decreased by 0.8–2.0%	Structured training; site rotation	6 months
Smith (2017)[29]	LH detected in study cohort (n=75)	ND	ND	HbA1c improved; insulin dose reduced by 5.6 IU/day	2×45min training; 4mm needles	3~6 months
Volkova (2019)[20]	82.9% LH detection rate (n=140)	Partial resolution	ND	HbA1c decreased by 1.84%; BMI decreased by 3.25 kg/m^2	Proper injection; site rotation	6 months
Misnikova (2017)[30]	120 randomized patients	ND	ND	HbA1c decreased by 0.75% in training group	Structured training; 4mm needles	6 months
Ortiz-Roa (2017)[31]	Single case: prominent, pigmented	ND	ND	Glycemic improved	Technique guidance; avoid LH	10 days ~ 11 months
Gentile (2018)[32]	Single case: Two major LH at the two sides of the navel (9×8cm and 8×6cm)	Intranodular fluid got ultrasound-undetectable	Lesions shrunk slightly (6×6 cm on the right and 5×5 cm on the left) and got less wrinkled/pigmented	HbA1c decreased by 2.1%; insulin reduced by about 30%	Proper injection technique	6~12 months
Bertuzzi (2017)[11]	LH primarily in the abdomen of all patients (n=20), with clinical measurements averaging 30±15 cm² and ultrasound measurements of 35 ±10 cm², showing cutaneous thickness of 2.4±0.4 mm and subcutaneous thickness of 24.5±10.9 mm.	Iso-hyperechogenic with fibrotic component (n=6) Isoechogenic with mixed component (n=9) Iso-hypoechogenic without fibrotic segments (n=5)	1/10(10.0%) patient showed a 9mm decrease in LH thickness; 2/10 (20.0%) patients demonstrated increases of 12mm and 18mm respectively.	HbA1c decreased by 0.2%; No significant change in total insulin dose	Advising patients to avoid insulin injections in LH areas	3~12 months

Abbreviations: LH, insulin-induced lipohypertrophy; HbA1c, glycated hemoglobin; BMI, body mass index; ND, No Data reported.

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examination in LH diagnosis. The current study analysis shows that physical examination detection rates ranged from 27.9% to 79.7% (median 55.3%), while ultrasound detection rates were significantly higher, reaching 57.6–100% (median 82.9%). This substantial difference in detection rates may be attributed to multiple factors: first, variations in examiner experience and technical expertise; second, patient physical characteristics (such as BMI) potentially affecting palpation accuracy; and finally, differences in diagnostic criteria across studies. Notably, 9 studies[9,18–20,22–25,28] reported subclinical LH with prevalence ranging from 13% to 55%, indicating that reliance on physical examination alone may miss a considerable proportion of LH cases. This finding aligns with previous research, such as Lin et al's study[22] showing ultrasound detected 22.5% more LH cases than physical examination, while Volkova et al's research[20] demonstrated this difference could reach 55%.

Agreement analysis between the two examination methods showed κ values ranging from 0.129 to 0.99. Through methodological quality analysis, we found that study reporting higher agreement (Gentile 2020, κ=0.99)[19] employed standardized examination protocols and experienced examiners, while studies with lower agreement (such as Ucieklak 2022, κ=0.129)[28] may have had less rigorous examination procedures. This disparity emphasizes the importance of establishing standardized examination protocols.

The current study analysis identified typical ultrasound characteristics of LH: location in subcutaneous fat layer, well-defined borders, absence of capsule, and decreased blood supply, classified into nodular, diffuse, and hypoechoic types based on echo patterns.[10,19,27,28] These classification proportions are consistent with previous single-center studies. Ultrasound examination further revealed that LH involves not only local adipose tissue proliferation but also broader tissue changes, including subcutaneous tissue thickening,[18] connective tissue distortion,[22,23] and interstitial edema.[10] Some studies identified hypoechoic areas within lesions,[1] suggesting potential tissue necrosis, providing new perspectives for understanding LH pathophysiology.

LH ultrasound characteristics reveals complex tissue changes beyond simple nodule formation.[33] The heterogeneous echo patterns suggest different pathological stages, from early edematous changes to late fibrotic transformation.[9] The consistent finding of reduced vascularity across studies indicates significant tissue remodeling and may explain altered insulin absorption.

The diversity of ultrasound presentations suggests different developmental stages of LH. Currently, three classification[1,10,11] systems have been proposed, each with different emphasis but lacking unified standards. These grading systems share some common features while maintaining their unique characteristics. All classifications are based on ultrasound echogenic patterns and recognize both nodular and diffuse presentations of LH. However, they differ significantly in their approach to categorization. Bertuzzi's[11] system focuses primarily on histopathological changes, emphasizing the presence of fibrotic components and edema. Yu's[10] classification is more oriented toward echo characteristics and their patterns, while Hashem's[1] system introduces quantitative size measurements as a key differentiating factor. This diversity in approaches reflects the complex nature of LH and the different clinical perspectives in its evaluation.

The various grading systems provide valuable insights into the natural history and potential resolution of LH lesions. Early-stage LH, particularly nodular hyperechoic lesions, typically shows better potential for spontaneous resolution when insulin injections are discontinued at the affected sites. Diffuse LH patterns generally indicate a more established condition requiring longer periods of site avoidance and more intensive monitoring. Hypoechoic lesions, particularly those with evidence of tissue necrosis, show the poorest prognosis and may require surgical intervention.[10] Although this progression model has preliminary evidence, more prospective studies are needed for validation.

Regarding healing processes, different types showed significant variations. Nodular hyperechoic type showed the best prognosis, while diffuse and hypoechoic types showed poorer outcomes. This difference may relate to lesion duration and tissue damage extent. Gentile et al[32] first discovered insulin accumulation within LH lesions, providing a pathological basis for explaining glucose fluctuations and hypoglycemia occurrence. Regarding metabolic impacts, we found different LH types affected glycemic control differently.[11,29,31] After cessation of injection at lesion sites, nodular hyperechoic type patients showed mean HbA1c reductions of 0.8%,[10] while diffuse and hypoechoic type patients showed more significant improvements with HbA1c reductions of 1.5–2.0%. Daily insulin requirements generally decreased by 5.6–30%, with improved time in range and reduced coefficient of variation.[12,29]

All studies emphasized the importance of early detection and standardized injection. Smith et al[29] demonstrated significant improvement in patient outcomes through structured training, further confirmed by Misnikova et al[30] randomized controlled trial, indicating that LH is preventable and controllable.

This study has several limitations: methodological heterogeneity among studies; short follow-up periods (≤6 months); lack of standardized ultrasound assessment criteria and evaluation of different equipment and operator experience effects; limited research on hypoechoic type LH; absence of grey literature search and absence of cost-effectiveness analysis. These limitations suggest directions for future research.

Future research should focus on: conducting large-scale prospective studies to validate LH progression patterns; establishing unified ultrasound examination and assessment standards; exploring factors affecting LH prognosis; evaluating long-term effects of different interventions; and performing cost-effectiveness analyses. Particularly, more research is needed on hypoechoic type LH to clarify its pathological mechanism and optimal treatment strategies.

Conclusion

In conclusion, this systematic review demonstrates three key findings: (1) ultrasound examination shows significantly higher detection rates (57.6–100%) than physical examination in LH diagnosis; (2) different LH types present distinct ultrasound characteristics, with nodular hyperechoic (65.5%), diffuse hyperechoic (27.5%), and hypoechoic (7.0%) patterns; and (3) these different types show varying prognostic features and metabolic improvements. These findings provide an important basis for individualized diagnosis and treatment of insulin injection-related complications. Future high-quality research is needed to enhance our understanding of this important complication.

Ethics

This research did not require ethical approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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