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INSULIN-INDUCED LIPOHYPERTROPHY: INSIGHTS FROM THE ITALIAN CARE MODEL—DIAGNOSIS, PROGRESSION, CLINICAL IMPACT, CURRENT CHALLENGES, FUTURE PERSPECTIVES, AND THE REHABILITATIVE ROLE OF EDUCATION

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SUMMARY

Insulin-induced skin lipohypertrophy (LH) represents a highly prevalent yet frequently neglected localized complication of subcutaneous insulin therapy. Drawing extensively from the highly structured, three-tiered Italian diabetes care model, this comprehensive narrative review evaluates the current literature on the diagnostic criteria, prevalence, clinical consequences, pathogenesis, and treatment of LH. The Italian framework—characterized by a widespread network of territorial specialist centers (Second Level care)—provides unique real-world data on this phenomenon. Diagnosis of LH relies heavily on structured clinical examination and skin ultrasound, facilitated by specialized outpatient settings. Morphologically, LH disrupts insulin pharmacokinetics, precipitating erratic absorption, unexplained severe hypoglycemia, and extreme glycemic variability. These clinical events impose a massive economic burden on acute hospital care (Third Level). A global epidemic of injection errors highlights an alarming deficit in injection technique knowledge, not only among patients but also among healthcare professionals. Prevention and treatment hinge on strict adherence to proper injection techniques and the transition to ultra-thin 3.5mm/34G needles, which significantly reduce penetration force and improve patient adherence. However, technological advancement alone is insufficient: continuous, multimodal therapeutic educational rehabilitation—a core mandate of Italian territorial diabetes centers—is essential to regress LH lesions and restore metabolic control. Addressing these unmet needs globally requires updating international guidelines, such as the upcoming 2025 recommendations, while looking to the Italian integrated care model as a benchmark for the systemic implementation of standardized training.

KEYWORDS: Insulin therapy, Lipohypertrophy, Injection technique, Hypoglycemia, Glycemic variability, Therapeutic education, needle technology, Italian care model, Injection errors, Health economics.

INTRODUCTION

Since the advent of insulin therapy over a century ago, localized skin reactions at injection sites have been recognized as a persistent clinical challenge.[1,2] These reactions, broadly termed lipodystrophies (LD), encompass two distinct morphological and pathophysiological entities: lipoatrophy (LA) and lipohypertrophy (LH) [1]. Historically, LA—characterized by a deep, retracted scarring of the subcutaneous fatty tissue—was relatively common and primarily attributed to immunological responses to impurities in early animal-derived insulin preparations.[1,2] With the widespread adoption of highly purified human insulins, the prevalence of LA has plummeted to approximately 1–2%, making it a rare clinical entity.[1]

In stark contrast, lipohypertrophy (LH) has emerged as the dominant cutaneous complication, currently affecting an estimated 37% to over 60% of insulin-treated patients.[1,3] LH presents as a thickened, rubbery, and often firm swelling of the subcutaneous adipose tissue.[1] Unlike LA, LH is fundamentally driven by the potent local anabolic properties of insulin, exacerbated by mechanical trauma from improper injection techniques such as failing to rotate injection sites and repeatedly reusing needles.[1,4]

The magnitude of this problem is deeply intertwined with the global diabetes epidemic.[4] This growing patient population is particularly vulnerable to injection-site complications due to widespread insulin adherence barriers, including injection fatigue and needle fear.[5] The persistence of LH highlights a critical gap in global diabetes management: the frequent neglect of injection technique education by healthcare providers.[6,7] Effectively addressing these barriers requires not just new delivery devices, but a structured healthcare delivery system capable of providing continuous, specialized education and monitoring.[7,8]

The Italian Diabetes Care Model: A Rationale for Source Selection

The Italian National Health Service (Servizio Sanitario Nazionale, SSN) operates on a fundamentally universalistic principle. In the field of diabetology, this system is uniquely characterized by a highly organized, widespread network of specialized structures dedicated exclusively to the continuous care of patients with diabetes. Consequently, diabetes care in Italy is strictly stratified into a synergistic, three-tiered integrated care model:[9]

- **The First Level (Primary Care):** Entrusted to General Practitioners (GPs), this level is tasked with population screening, early diagnosis, the management of uncomplicated type 2 diabetes, and the initial referral of patients to specialists.
- **The Second Level (Territorial Specialist Centers):** This is the cornerstone of Italian diabetes care, comprising a widespread national network of outpatient diabetology clinics. These centers have a specific operational mandate to manage complex clinical cases, initiate and titrate complex therapies (such as insulin regimens), deliver continuous and structured therapeutic education (including proper injection techniques), and manage the early stages of chronic complications.
- **The Third Level (Hospital Care):** This level is strictly reserved for acute settings, focusing on the management of severe metabolic emergencies (e.g., severe hypoglycemia, ketoacidosis) and the treatment of advanced, end-stage chronic complications that require multidisciplinary or surgical interventions.[9]

Furthermore, the operational performance and quality of care within this specialized network are systematically and rigorously monitored through periodic national clinical reports. Most notably, the Annali AMD (Annals of the Association of Medical Diabetologists) initiative has, for over 20 years, continuously audited the clinical activities, outcomes, and quality indicators of territorial specialist centers, working in close collaboration with Italian national health institutions.[10]

Methods of Analysis

Given the structural advantages of the Italian three-tiered diabetology network, which provides a highly monitored, specialized, and data-rich territorial environment, the methodology of this narrative review intentionally prioritizes data generated from this framework. Italian clinical study groups produce a robust, uniquely detailed, and unmatched volume of real-world epidemiological data regarding outpatient insulin management, therapeutic education, and injection-site complications.

Therefore, this review synthesizes data from multi-center observational surveys, randomized controlled trials, and consensus statements focusing on insulin injection techniques within this setting. Key sources include the HYPOS-1 study,[11] the intensive structured education-based rehabilitation protocols (ISTERP 1, 2, and 3 studies),[12,13] the critical laboratory findings from the PICASSO study,[14] and recent crossover randomized non-inferiority trials like the AGO 02 study.[15] Literature reviewed covers cohorts ranging from small clinical validation groups to large-scale longitudinal studies assessing clinical, histopathological, capillaroscopic, and health-economic outcomes associated with lipohypertrophy, bruising, and correct needle usage.[1,14,16,29,47,48,49,50,51] Starting with the Italian care model, the review opens up to more general assessments from around the world to examine the critical issues in greater detail.

Pathogenesis and Histopathology

The pathogenesis of insulin-induced lipohypertrophy is multifactorial, integrating mechanical, pharmacological, and potentially local microvascular elements.[1,17]

Insulin as an Anabolic Agent. Insulin is a potent local growth factor. Continuous, high-concentration exposure of subcutaneous tissue to exogenous insulin stimulates both the proliferation and differentiation of pre-adipocytes.[1]

This local lipogenic effect is the primary driver of tissue expansion and fat accumulation in LH lesions.

Mechanical Trauma and Thermal Stress. Mechanical trauma significantly compounds the pharmacological effects of insulin.[1] The repeated insertion of needles into a restricted skin area causes repetitive micro-injury.[16] Within the Italian territorial network, multivariate analysis of large patient cohorts has demonstrated strong correlations between these erroneous injection habits and acute risks.[13] Specifically, missing injection site rotation is strongly associated with LH presence (Odds Ratio [OR] 9.30, 95% CI: 5.79–14.93, $p < 0.001$)[13] and increases the risk of severe hypoglycemia (SeH) with a Relative Risk (RR) of 3.67.[13] This damage is exacerbated by needle reuse, which drastically heightens the risk of both severe (RR 3.46) and symptomatic hypoglycemia (RR 4.74).[13] Furthermore, the injection of ice-cold insulin elevates the risk of severe hypoglycemia (RR 3.39).[12,13]

Histopathological Findings. Histopathological examination reveals an altered tissue architecture. Grossly, the lesions consist of yellowish, unencapsulated material with markedly decreased vascularity.[17] Hematoxylin-eosin staining reveals an excess of mature adipocytes within the dermal reticular layer.[17] Adipocytes within LH lesions are significantly hypertrophic, reaching diameters of 100 to 200 μm (compared to 70–90 μm in normal tissue).[17]

Electron microscopy reveals dense fibrous striae infiltrating the adipose tissue, creating a rigid, compartmentalized structure.[17]

Microvascular Alterations and Videocapillaroscopy. Studies utilizing nailfold videocapillaroscopy (NVC) indicate that while patients with LH exhibit classical diabetic microangiopathy, these specific capillaroscopic patterns do not differ significantly from those in diabetic patients without LH.[18] Severe NVC abnormalities correlate strongly with chronically elevated HbA1c levels (>9.0%), suggesting that microvascular deterioration is a reflection of overall poor metabolic control rather than a direct pathogenetic precursor to LH.[18]

Morphological Evolution

The development of lipohypertrophy is increasingly understood as a continuous pathophysiological spectrum moving from acute mechanical injury to a chronic, end-stage fibrotic mass:

- **Stage 1 (Acute Injury & Inflammation):** Localized micro-hemorrhages and a mild inflammatory response due to repetitive micro-trauma.[16,19]
- **Stage 2 (Lipogenesis & Hypertrophy):** Massive adipocyte hypertrophy and hyperplasia.[17,19]
- **Stage 3 (Fibrosis & Apoptosis):** Progressive collagen deposition and cellular apoptosis leading to dense, avascular fibrous striae.[17,20]
- **Stage 4 (End-Stage Nodule Formation):** Mature, fibrotic plastrons harboring supra-physiological concentrations of unabsorbed insulin.[17,20]

The extreme endpoint of this evolutionary model—often a result of patients failing to access continuous Second Level territorial education early on—is illustrated by a "monster case" of LH presenting as a massive abdominal mass.[19]

Over a 3-year follow-up under strict conservative management, the mass demonstrated significant initial softening (reversibility of hypertrophic adipocytes).[19] However, the dense fibrotic scaffolding failed to fully regress, transitioning into a deflated fibrotic sac.[20] This highlights that advanced fibrotic LH lesions cross a threshold of irreversibility, raising the clinical dilemma of when to abandon educational rehabilitation in favor of Third Level surgical interventions.[19,20]

Diagnostic Criteria and Clinical Identification

In the context of specialized outpatient clinics (Second Level), the accurate diagnosis of LH relies on a structured sequence of inspection and palpation, a practice often missed in non-specialized settings.[1,2] Palpation is the cornerstone of diagnosis, utilizing slow, circular, and vertical fingertip movements, followed by the "pinching maneuver" to differentiate the thickened, rubbery texture of an LH lesion from normal fat.[2] Skin ultrasonography (USS) serves as the gold standard reference method, easily integrated into specialist settings to reveal hyperechoic fibrous striae within the localized thickening of the subcutaneous adipose layer.[21,22]

Comparative Diagnostic Performance

Large-scale clinical evaluations confirm that while clinical examination is convenient, ultrasound scanning (USS) detects a significantly higher number of subclinical LH lesions.

Table 1: Sensitivity and Specificity of Diagnostic Modalities for Lipohypertrophy. *Note: Low specificity of USS compared to clinical examination reflects USS's ability to detect subclinical LH lesions invisible during standard clinical assessment.[21]

YEAR	FIRST AUTHOR	SUJECTN	DIAGNOSTIC METHOD	SENSITIVITY	SPECIFICITY	REF.
2021	Yu J.	382	Ultrasound Scanning (USS) (vs. Clinical Exam)	94.3%	32.0%*	[21]
2021	Yu J.	382	Clinical Examination (vs. USS as standard)	79.0%	67.3%	[21]
2021	Wang W.	506	Ultrasound Scanning (USS)	~100%	N/A (Gold Standard)	[22]
2016	Gentile S.	60	Structured Palpation (Trained Professionals)	>90%	>85%	[2]

Prevalence and Epidemiology

Epidemiological data on LH prevalence exhibit extreme variability.[1] However, thanks to the standardized auditing of territorial centers utilizing structured palpation, the prevalence consistently hovers between 40% and 50%.[13]

Table 2: ***Comparison of Lipohypertrophy Frequency Across Selected Studies.***

First Author	Year	Journal	Subjects (n)	Diagnostic Method	Ref.
Hauner H.	1996	Exp Clin Endocrinol Diab	233	Clinical examination	[23]
Partanen T.	2000	Pract Diab Int	Not specified	Not specified	[24]
Kordonouri O.	2002	Diab Care	Not specified	Clinical examination	[25]
Vardar B.	2007	Diab Res Clin Pract	215	Clinical examination	[26]
Blanco M.	2013	Diab Metab	Not specified	Clinical examination	[3]
Al Ajlouni M.	2015	Int J Endocrinol Metab	1,090	Clinical inspection	[27]
Gentile S.	2016	Diab Ther	780	Palpation & US confirmation	[16]
Gentile S.	2021	Diab Ther	318	Structured inspection	[12]
Gentile S.	2022	Adv Ther	713	Structured exam & US scan	[13]

Clinical Consequences

The close clinical monitoring available in specialized territorial centers clearly illustrates how LH severely disrupts glycemic control.

Erratic Insulin Pharmacokinetics and the "Reservoir Effect". The avascular, fibrotic nature of LH tissue severely delays the systemic absorption of insulin. Insulin injected into LH tissue exhibits blunted peak action, reduced absorption by 20–40%, and a massive increase in intra-subject absorption variability.[8] Clinically, this "reservoir effect" leads to inadequate postprandial insulin coverage.[7] Unexpected hyperglycemia and erratic glycemic swings managed in outpatient settings are frequently traced back directly to pen and needle errors rather than physiological insulin resistance.[28]

Hypoglycemia and Glycemic Variability. The 2025 Standards of Care emphasize aggressively minimizing the risk of hypoglycemia.[29] Patients injecting into LH nodules experience vastly higher rates of unexplained hypoglycemia.[1,7]

Large abdominal LH lesions (diameter > 4 cm) more than triple the risk of severe hypoglycemia (RR 3.38).[13]

Overall, LH lesions are significantly associated with high glycemic variability (OR 2.32, $p < 0.001$) and the onset of unexplained hypoglycemic episodes (OR 2.35, $p = 0.001$).[13] Consequently, the incidence of severe hypoglycemia (SeH)—events requiring immediate Third Level hospital care—is markedly elevated.[12,13]

Economic Burden

From the perspective of the Italian National Health Service (SSN), the economic consequences of LH-driven hypoglycemia represent a massive strain on acute resources.[12,13] Severe hypoglycemic events force patients out of Second Level territorial management and into expensive Third Level hospital interventions. Cost analyses demonstrate:

- Physician Home Visit (PHV): €25.82.[12,13]
- Emergency Room (ER) visit and treatment: €241.00.[12,13]
- Emergency Medical Services (EMS) utilization: €128.50 per hour.[12,13]
- Hospitalization Cost (HC): €5,025 (based on 6.7 days average stay at €750/day).[12,13]

In dedicated studies leveraging intensive territorial education, six-month costs generated by severe hypoglycemia (EMS, ER visits) plummeted from €77,107.50 to €13,045.50 (-83.08%, $p < 0.00001$).[13] Abandoning injections into fibrotic nodules also enabled a daily insulin dose (DID) reduction of up to 24% at 12 months ($p < 0.05$),[13] translating to immense systemic drug procurement savings.[12]

The Spectrum of Injection Errors and Educational Gaps

The persistence of injection-site complications is largely fueled by a global prevalence of injection errors. Patients frequently exhibit bizarre or dangerously incorrect injection behaviors,[30,31] ranging from inappropriate site selection to the extreme consequence of reused needles breaking off and remaining embedded in the body.[32]

Furthermore, the incorrect technical operation of modern insulin pen devices is a frequent cause of severe, unexpected hyperglycemia.[28,33,34,35] Crucially, these patient errors are directly linked to insufficient or entirely absent clinic-based education.[30,34]

A growing body of literature highlights an alarming global deficit in injection technique knowledge among healthcare professionals (HCPs).[36,37] This educational gap is systemic, spanning physicians,[38] nurses,[39,40] and pharmacists.[43,44] Nationwide surveys across diverse populations, including China and India, emphasize that what HCPs fail to know or properly teach directly translates into poor patient practices and the subsequent onset of clinical complications.[41,42] Therefore, addressing these ubiquitous errors requires a paradigm shift: before patient behaviors can be durably corrected, standardized training must be systematically implemented for all healthcare providers to close these critical educational gaps. Randomized controlled trials have unequivocally shown that doing so effectively improves overall glycemic control and drastically reduces the incidence of lipohypertrophy.[45, 46]

Evolution, Prevention, and Treatment

Technological Interventions: The Paradigm Shift to 3.5mm/34G Needles. Historically, 4mm, 32G needles were the gold standard to safely deposit insulin into the subcutaneous space.[47,48] However, over a century of innovation, the widespread diffusion of the 3.5 mm, 34G needle represents a significant leap forward.[14,15,49] The **PICASSO study** provided laboratory evidence demonstrating that 34G x 3.5mm needles require a significantly lower maximum penetration load.[14] A crossover randomized non-inferiority trial confirmed the efficacy, safety, and high acceptability of these needles in routine clinical practice.[15] This reduction in penetration force is heavily influenced by advanced multi-bevel tip geometry.[14,50] Mitigating injection pain directly reduces the likelihood that patients will reuse needles or seek out the denervated areas of existing LH lesions, breaking the cycle of lipohypertrophy.[5,14,15,51]

Therapeutic Education on Injection Techniques: The Role of Territorial Centers. Over the past eight years, the paradigm of therapeutic education has evolved. Single educational interventions fail to induce lasting behavioral changes.[12,13] In large randomized trials, a control group receiving only a single session saw their needle reuse and intra-LH injection rates rebound to near-baseline levels (>90%) by 12 months.[13]

Conversely, the Second Level of the Italian care model—the territorial specialist centers—is uniquely equipped to deliver continuous, multimodal behavioral rehabilitation. When this approach is utilized, the rate of intra-LH injections collapses to 1.9% (vs. 59.9% in controls, $p < 0.001$).[12,13] Morphologically, LH lesion size was reduced by 65%.[13]

The rate of severe hypoglycemia plummeted from 16.4% to 0.6%.[12,13] Metabolically, HbA1c dropped significantly,[12] and glycemic variability was nearly halved.[12] This proves that combining technological advancements (34G needles) with the structural capacity of specialized territorial clinics to provide ongoing follow-ups and tactile training is highly effective.[12,13,15]

Other Injection-Site Reactions: Bruising and Non-Insulin Drugs

Bruising occurs in roughly 33.2% of insulin-treated patients, primarily a mechanical phenomenon resulting from excessive pressure exerted on the pen device.[16] While isolated bruising does not alter insulin pharmacokinetics,[16] territorial centers track it as a critical visual indicator of injection technique errors and an early mechanical precursor to LH.[16] Furthermore, lipodystrophic reactions occur with other subcutaneous therapeutics (e.g., GLP-1 RAs, anti-TNF agents), highlighting the need to apply insulin-standard injection protocols across all injectables.[1]

Limitations of Current Evidence

While the Italian three-tiered system provides excellent data from Second Level specialist centers, integrating these rigorous structured protocols into under-resourced First Level primary care settings poses ongoing logistical challenges.[12,13] Additionally, data on behavioral adherence often relies on patient self-reporting, which is subject to recall bias.[13] The exact pathophysiological mechanism bridging bruising and fibrotic LH requires further study.[16]

Another limitation is the scarcity of information on clinical outcomes and the lack of systematic and timely linkage to administrative databases capable of generating additional information, for example, on actual drug consumption, the extent of services provided within other medical disciplines, and the overall course of the disease. A major government initiative is currently underway to create a computerized national health record, which we hope will significantly contribute to the integration of the various databases.

Unmet Needs and Future Perspectives: Updating the Recommendations

Addressing LH requires systemic HCP training and reimbursement models that financially incentivize diabetes care teams to conduct intensive educational sessions.[13,52] In light of technological advancements, the upcoming **actual recommendations**—which currently endorse 4 mm needles[53] could be updated to formally integrate the 3.5 mm/34G needle as a preferred choice. Explicitly acknowledging how advanced tip geometry reduces penetration force and enhances patient comfort is a critical catalyst in securing long-term adherence.[14,15] Even in this case, however, randomized, blinded clinical studies are needed to definitively validate whether the subjective preference of diabetic injectors for this innovative needle is supported by objective data.

CONCLUSIONS

Insulin-induced skin lipohypertrophy fundamentally distorts drug absorption, unleashing unpredictable glycemic volatility and life-threatening hypoglycemia that directly burden acute hospital systems. The Italian care model demonstrates that eradicating LH requires a paradigm shift: technological solutions like the 3.5mm/34G needle must be embedded within a structured healthcare delivery system. Establishing widespread territorial specialist centers capable of delivering continuous, multimodal educational rehabilitation is essential. By elevating injection technique education to the same level of clinical importance as the prescription of the insulin itself, healthcare systems globally can drastically improve metabolic outcomes and reduce economic waste.

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REFERENCES

1. Gentile S, Strollo F, et al. Injection-Related Local Side Effects in the Treatment of Diabetes Mellitus: A Methodological Approach and Possible Solutions. Consensus Statement. SMGroup e-books, 2016.
2. Gentile S, Guarino G, Giancaterini A, Guida P, Strollo F. A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. Springerplus, 2016; 5: 563.

3. Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab, 2013; 39(5): 445-453.
4. IDF Atlas 11th English Edition 2025. Global Diabetes Data & Statistics.
5. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med, 2012; 29(5): 682-689.
6. Gentile S, Guarino G, Satta E, et al. A Journey through Guidelines, Consensus, Curriculum of Educators and Clinical Practice on Insulin-Induced Skin Lipohypertrophy: From the Earth to the Moon. Med Res Arch, 2022; 10(9).
7. Gentile S, Strollo F, Della Corte T, Marino G, Guarino G. Insulin related lipodystrophic lesions and hypoglycemia: Double standards? Diabetes Metab Syndr, 2018; 12(5): 813-818.
8. Famulla S, Hövelmann U, Fischer A, et al. Insulin injection into lipohypertrophic tissue: blunted and more variable insulin absorption and action and impaired postprandial glucose control. Diabetes Care, 2016; 39(9): 1486-1492.
9. Italian Ministry of Health. Piano sulla Malattia Diabetica. State-Regions Agreement Rep. N. 14/CSR, 2012.
10. Rossi MC, Nicolucci A, Di Bartolo P, et al. The AMD Annals initiative: A 20-year journey of continuous quality improvement in diabetes care in Italy. Diabetes Res Clin Pract, 2022; 186: 109825.
11. Giorda CB, Rossi MC, Ozzello O, et al. Healthcare resource use, direct and indirect costs of hypoglycemia in type 1 and type 2 diabetes, and nationwide projections. Results of the HYPOS-1 study. Nutr Metab Cardiovasc Dis., 2017; 27(3): 209-216.
12. Gentile S, Guarino G, Della Corte T, et al. Role of Structured Education in Reducing Lypodistrophy and its Metabolic Complications in Insulin-Treated People with Type 2 Diabetes: A Randomized Multicenter Case-Control Study. Diabetes Ther, 2021; 12(5): 1379-1398.
13. Gentile S, Guarino G, Della Corte T, et al. The Economic Burden of Insulin Injection-Induced Lipohypertophy. Role of Education: The ISTERP-3 Study. Adv Ther, 2022; 39(5): 2192-2207.
14. Leonardi L, Viganò M, Nicolucci A. Penetration force and cannula sliding profiles of different pen needles: the PICASSO study. Med Devices (Auckl), 2019; 12: 311-317.
15. De Berardis G, Scardapane M, Lucisano G, et al. Efficacy, safety and acceptability of the new pen needle 34 G × 3.5 mm: A crossover randomized non-inferiority trial; AGO 02 study. Curr Med Res Opin, 2018; 34(12): 1699-1704.
16. Gentile S, Guarino G, Della Corte T, et al. Bruising: A Neglected, Though Patient-Relevant Complication of Insulin Injections Coming to Light from a Real-Life Nationwide Survey. Diabetes Ther, 2021; 12(4): 1143-1157.
17. Fujikura J, Fujimoto M, Yasue S, et al. Insulin-induced lipohypertrophy: report of a case with histopathology. Endocr J., 2005; 52(5): 623-628.
18. Gentile S, Guarino G, Cuomo G, et al. Videocapillaroscopy, Insulin-Induced Skin Lipohypertrophy, and Bruising: A Preliminary Approach. J Diabet Res Rev Rep, 2021; 3(2): 1-4.
19. Gentile S, Guarino G, Strollo F. How to treat improper insulin injection-related lipohypertrophy: A 3-year follow-up of a monster case and an update on treatment. Diabetes Res Clin Pract, 2021; 171: 108534.
20. Gentile S, Guarino G, Strollo F. Unexpected evolution of a monster case of insulin-induced skin lipohypertrophy. Diabetes Res Clin Pract, 2023; 206: 110994.

21. Yu J, Wang H, Zhu M, et al. Detection sensitivity of ultrasound scanning vs. clinical examination for insulin injection-related lipohypertrophy. Chin Med J (Engl), 2021; 135(3): 353-355.
22. Wang W, Huang R, Chen Y, Tu M. Values of ultrasound for diagnosis and management of insulin-induced lipohypertrophy: A prospective cohort study in China. Medicine (Baltimore), 2021; 100(30): e26743.
23. Hauner H, Stockamp B, Haastert B. Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. Exp Clin Endocrinol Diabetes, 1996; 104(2): 106-110.
24. Partanen T, Rissanen A. Insulin injection practices. Pract Diabetes Int., 2000; 17(8): 252-254.
25. Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. Diabetes Care, 2002; 25(3): 634.
26. Vardar B, Kizilci S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. Diabetes Res Clin Pract, 2007; 77(2): 231-236.
27. Al Ajlouni M, Abujbara M, Batieha A, Ajlouni K. Prevalence of lipohypertrophy and associated risk factors in insulin-treated patients with type 2 diabetes mellitus. Int J Endocrinol Metab, 2015; 13(2): e20776.
28. Strollo F, Guarino G, Gentile S. Unexpected Hyperglycemia? Check the Pen and Needle! An Opportunity to Prevent Injection Technique Errors and Find Causes and Possible Solutions. Diabetology. 2025;6:89.
29. American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2025. Diabetes Care, 2025; 48: S128–S145.
30. Wei ET, Koh E, Kelly MS, Wright LA, Tylee TS. Patient errors in use of injectable antidiabetic medications: A need for improved clinic-based education. J Am Pharm Assoc, 2020; 60: e76–e80.
31. Briatore L. Insulin: Where, how, how much?, or: The most bizarre ways to (not) inject insulin. Il G. AMD, 2015; 18: 197–199.
32. Qiao YJ, Xin-Yuan Y, Xu RL, et al. Effect of a reused insulin needle remaining in a patient’s body. J Diabetes Investig, 2023; 14: 821–823.
33. Institute for Safe Medication Practices. Severe Hyperglycemia in Patients Incorrectly Using Insulin Pens at Home, 2018.
34. Truong TH, Nguyen TT, Armor BL, Farley JR. Errors in the Administration Technique of Insulin Pen Devices: A Result of Insufficient Education. Diabetes Ther, 2017; 8: 221–226.
35. Trief PM, Cibula D, Rodriguez E, Akel B, Weinstock RS. Incorrect insulin administration: A problem that warrants attention. Clin Diabetes, 2016; 34: 25–33.
36. Spollett G, Edelman SV, Mehner P, Walter C, Penfornis A. Improvement of insulin injection technique: Examination of current issues and recommendations. Diabetes Educ, 2016; 42: 379–394.
37. Hirsch LJ, Strauss KW. The injection technique factor: What you Don’t know or teach can make a difference. Clin Diabetes, 2019; 37: 227–233.
38. Shen M, Shi Y, Zheng S, Fan H, Xu J, Yang T. A Systematic Survey of Physicians’ Insights into Lipohypertrophy. Front Public Health, 2021; 9: 738179.
39. Wu X, Zhao F, Zhang M, et al. Insulin Injection Knowledge, Attitudes, and Practices of Nurses in China: A Cross-Sectional Nationwide Study. Diabetes Ther, 2021; 12: 2451–2469.
40. Liao Y, Liu X, Huang J, Chen Q, Li N, Zhou P. Insulin injection knowledge, attitude and behaviour of nurses: A cross-sectional study in Guangdong Province. Nurs Open, 2023; 10: 3754–3765.

41. Guo L, Zhang Q, Xue Y, et al. A Nationwide Cross-sectional Survey of Knowledge and Practices of Diabetes Drug Injection Techniques of Patients, Nurses, and Physicians: The China IT Improve Study. Mayo Clin Proc, 2023; 98: 1482–1500.
42. Kalra S, Mithal A, Sahay R, et al. Indian Injection Technique Study: Injecting Complications, Education, and the Health Care Professional. Diabetes Ther, 2017; 8: 659–672.
43. Wang J, Pei Y, Yu F, Kang Z, Zheng Y. Understandings, Attitudes, and Barriers About Diabetes Care: Analysis of Factors Influencing Community Pharmacists in China. Diabetes Metab Syndr Obes, 2021; 14: 1999–2009.
44. Abdelaziz TA, Abdulraheem MA, Badi SA, et al. Knowledge, attitude and practice of Sudanese pharmacist with regard to management of diabetes during Ramadan: A cross-sectional survey. Diabetes Metab Syndr, 2019; 13: 122–126.
45. Misnikova IV, Gubkina VA, Lakeeva TS, Dreval AV. A randomized controlled trial to assess the impact of proper insulin injection technique training on glycemic control. Diabetes Ther, 2017; 8: 1309–1318.
46. Campinos C, Le Floch JP, Petit C, et al. An effective intervention for diabetic lipohypertrophy: Results of a randomised, controlled, prospective, multicentre study in France. Diabetes Technol Ther, 2017; 19: 623–632.
47. Hirsch LJ, Gibney MA, Li L, Bérubé J. Glycemic control, reported pain and leakage with a 4mm×32G pen needle in obese and non-obese adults with diabetes: A post hoc analysis. Curr Med Res Opin, 2012; 28(8): 1305–1311.
48. Hirsch L, Byron K, Gibney M. Intramuscular risk at insulin injection sites—Measurement of the distance from skin to muscle and rationale for shorter-length needles for subcutaneous insulin therapy. Diabetes Technol Ther, 2014; 16(12): 867–873.
49. Heinemann L, Nguyen T, Bailey TS, et al. Needle Technology for Insulin Administration: A Century of Innovation. J Diabetes Sci Technol, 2023; 17(2): 449-457.
50. De Tommasi F, Silvestri S. Influence of Insulin Pen Needle Geometry on Pain Perception and Patient's Acceptability: A Review. Technologies, 2024; 12: 233.
51. Mannucci E, Pintaudi B, Lunati ME, Fiorina P. Needle characteristics and the insulin injection experience in patients with diabetes. Acta Diabetol, 2025; 62: 1371–1393.
52. Gentile S, Strollo F. Cost saving effects of a short-term educational intervention entailing lower hypoglycaemic event rates in people with type 1 diabetes and lipo-hypertrophy. Diabetes Res Clin Pract, 2018; 143: 320-321.
53. Klonoff DC, Berard L, Franco DR, et al. Advance Insulin Injection Technique and Education With FITTER Forward Expert Recommendations. Mayo Clin Proc, 2025 Apr; 100(4): 682-699. doi: 10.1016/j.mayocp.2025.01.004. PMID: 40180487.