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Efficacy of Sound Touch Elastography in Assessing Subcutaneous Lipohypertrophy from Insulin Injections

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Objective: Lipohypertrophy (LH) is a localized complication of type 2 diabetes mellitus in patients on long-term insulin therapy. Sound touch elastography (STE) is a crucial tool in the quantitative real-time assessment of tissue hardness within specific target regions. This study aims to explore the efficacy of STE in evaluating the hardness of subcutaneous LH at insulin injection sites in individuals with type 2 diabetes mellitus and investigate the correlations between the hardness of LH lesions and various clinical indicators.

Methods: A cohort of 53 individuals with type 2 diabetes mellitus undergoing insulin therapy at the Department of Endocrinology, Affiliated People's Hospital of Ningbo University from April 2023 to January 2024 was selected. General clinical data of the participants and STE-derived Young's modulus hardness values of the LH lesions and adjacent normal adipose tissue were collected. The Wilcoxon signed-rank test was employed for comparative analysis between the two tissue groups, while Spearman's rank correlation was used to examine the relationships between Young's modulus values of the LH lesions and clinical indicators.

Results: Routine ultrasound examination revealed LH in all 53 participants. The maximum (E_{max}), average (E_{mean}), and minimum (E_{min}) values of Young's modulus significantly differed between the LH lesions and surrounding healthy adipose tissue ($Z=-6.334$, $P<0.001$; $Z=-6.263$, $P<0.001$; $Z=-5.865$, $P<0.001$, respectively), indicating greater hardness in the LH lesions. Additionally, the E_{min} values of the LH lesions were positively correlated with the glycated hemoglobin levels ($r=0.293$, $P<0.05$).

Conclusion: Ultrasound elastography-based STE exhibits great potential in assessing LH hardness in individuals undergoing insulin therapy for type 2 diabetes mellitus. STE offers a novel and objective ultrasonographic approach for accurately evaluating LH severity, highlighting the significance of this technique in clinical diagnostics.

Keywords: ultrasound elastography, type 2 diabetes, lipohypertrophy, insulin injections

Introduction

The most recent Global Diabetes Map published by the International Diabetes Federation has revealed that approximately 537 million adults are living with diabetes worldwide as of 2021, with China having the highest number of affected individuals.[1] The instability of blood glucose levels can substantially accelerate the development of various diabetes-associated complications, underscoring the value of achieving stable blood glucose levels in long-term diabetes management. Insulin injection therapy is an effective method to maintain stable blood glucose levels. However, researchers have indicated that individuals undergoing prolonged insulin therapy are at risk of developing subcutaneous lipohypertrophy (LH), a local complication, with an average LH rate of 41.8%.[2–4] LH is characterized by pathological alterations such as hypertrophy, degeneration, fibrosis, and reduced vascularity in the subcutaneous fat cells at insulin injection sites in individuals with diabetes.[5] These pathological changes can lead to decreased insulin efficacy, thereby causing unexpected episodes of hypoglycemia and postprandial hyperglycemia.[6]

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Earlier screening methods for LH have primarily relied on visual and tactile clinical examinations. However, this approach is highly subjective and can be substantially influenced by the examiner's expertise level. In recent years, LH research has shifted focus toward using high-frequency ultrasound as a screening technique due to its higher detection rate and objective evaluation of LH characteristics such as shape, distribution, size, and depth using ultrasound images.[7–9] However, current research on this approach predominantly explores the value of conventional two-dimensional ultrasound in detecting LH without providing quantitative data. Additionally, scarce studies have applied new ultrasound technologies to further examine the histological properties and severity of LH, while research on the correlation between LH and relevant clinical index variables is also lacking.

Sound touch elastography (STE) is a relatively new iteration of two-dimensional shear wave elastography-based ultrasound imaging technology. STE has emerged as a crucial tool in the quantitative real-time assessment of tissue hardness within specific target regions. Currently, the STE technique is widely utilized in assessing the tissue hardness of organs such as the liver and breast.[10,11] By integrating the histological features of LH, this study aimed to explore the utility of STE in quantitatively assessing the hardness of internal LH tissues and to investigate the correlation between LH hardness and relevant clinical indicators. We hope this study will expand the available imaging methods for assessing the internal LH features and provide an objective imaging basis for precisely evaluating LH severity.

Methods

Study Participants

This cross-sectional study included individuals with diabetes mellitus who visited or were hospitalized in the Department of Endocrinology at the Affiliated People's Hospital of Ningbo University, China between April 2023 and January 2024. The sample size was estimated by G power 3.1.9.2. The significance level was set at $\alpha = 0.05$ and the statistical test was two-tailed. For the efficacy statistic, the effect size was set to medium (0.5) and power to 0.9. The resulting minimum sample size required was 44 subjects. Participant inclusion criteria were as follows: 1). diagnosis of type 2 diabetes mellitus based on the 1999 World Health Organization criteria; 2). availability of complete general clinical data; and 3). history of or ongoing subcutaneous insulin therapy. Participant exclusion criteria were as follows: 1). history of skin or subcutaneous soft tissue neoplasms; 2). scars or surgical history at insulin injection sites; 3). concurrent malignancies or acute or chronic infections; 4). other severe chronic illnesses; 5). psychiatric disorders or communicative impairments; or 6). pregnancy or lactation. The subjects of this study were randomly selected, and 53 participants were finally included in this study. The study protocol was approved by the Ethics Committee of the Affiliated People's Hospital of Ningbo University (approval no.: 2023-SR-076). All participants included in this study provided written informed consent.

Collection of General Clinical Data

The clinical data of the included participants were meticulously obtained by professional clinical medical personnel who acquired the information by reviewing current medical records or conducting direct interviews. A standardized questionnaire was used for collecting the following data: age, gender, body mass index (BMI), diabetes duration, type of insulin injections used, daily dosage and frequency of injections, duration of continuous injections, and HbA_{1c} levels.

Ultrasound and STE Examinations of LH

The equipment utilized for the examination of LH included Mindray's Nuewa R9S and Resona R9G Platinum Edition high-end color Doppler ultrasound diagnostic devices equipped with L15-3WU high-frequency linear array probes (frequency: 3.8–15.4 MHz) and STE imaging functionality.

Routine Ultrasound Examination

After verifying the participant's identity, the participant was instructed to lie in a supine position and relax their abdominal muscles to fully expose the abdomen. The exposed abdomen was then scanned systematically from right to left and top to bottom to assess the echo conditions of the layers of the skin, subcutaneous fat, and superficial and deep fascia. The ultrasound diagnostic criteria for LH lesions were defined as follows:[12,13] 1). predominantly high echogenicity within the subcutaneous fat layer of the abdomen, with clear boundaries and nodular appearance either with or without a hypoechoic halo; 2). uneven echogenicity at the lesion site compared to the surrounding normal adipose tissue; 3). potential association with the

deformation of surrounding connective tissue; 4). insignificant blood flow signal; and 5). absence of cystic changes. A diagnosis of LH can be confirmed via ultrasound if at least four of the above five criteria are satisfied.[8] After LH lesions were identified, their echogenicity, shape, margins, and color Doppler flow were assessed.

STE Examination

After determining the largest section of the LH lesion, the ultrasound system was switched to the STE mode. With the scale set to 0–200 kPa, the sampling frame was adjusted in size and positioned over the area of interest to center the LH lesion and surrounding normal adipose tissue. Subsequently, the probe was gently placed on the participant's abdomen to avoid pressure, and the participant was instructed to breathe calmly and hold their breath at the end of an exhalation. After 2–5 s to ensure that the elastography image quality was stabilized (reliability index >90%) without notable artifacts, the image was frozen and the STE image was obtained. In the representative image in Figure 1, red indicates harder tissue, whereas blue denotes softer tissue. Moreover, measurement circle 1 is adjusted to cover the entire LH lesion as much as possible, while an equally sized measurement circle 2 is placed on surrounding normal adipose tissue as far away as possible from the LH lesion. Young's modulus is a measure of tissue stiffness, calculated from the external stress applied to an object and the strain caused by the stress. The maximum (E_{max}), minimum (E_{min}), and average (E_{mean}) values of Young's modulus of the two tissues were calculated and recorded, with the process repeated thrice to obtain an average value. Additionally, an extra STE examination was performed at a non-insulin-injected site on the participant's abdomen as an internal control, following the same steps. All ultrasound image data were recorded and stored.

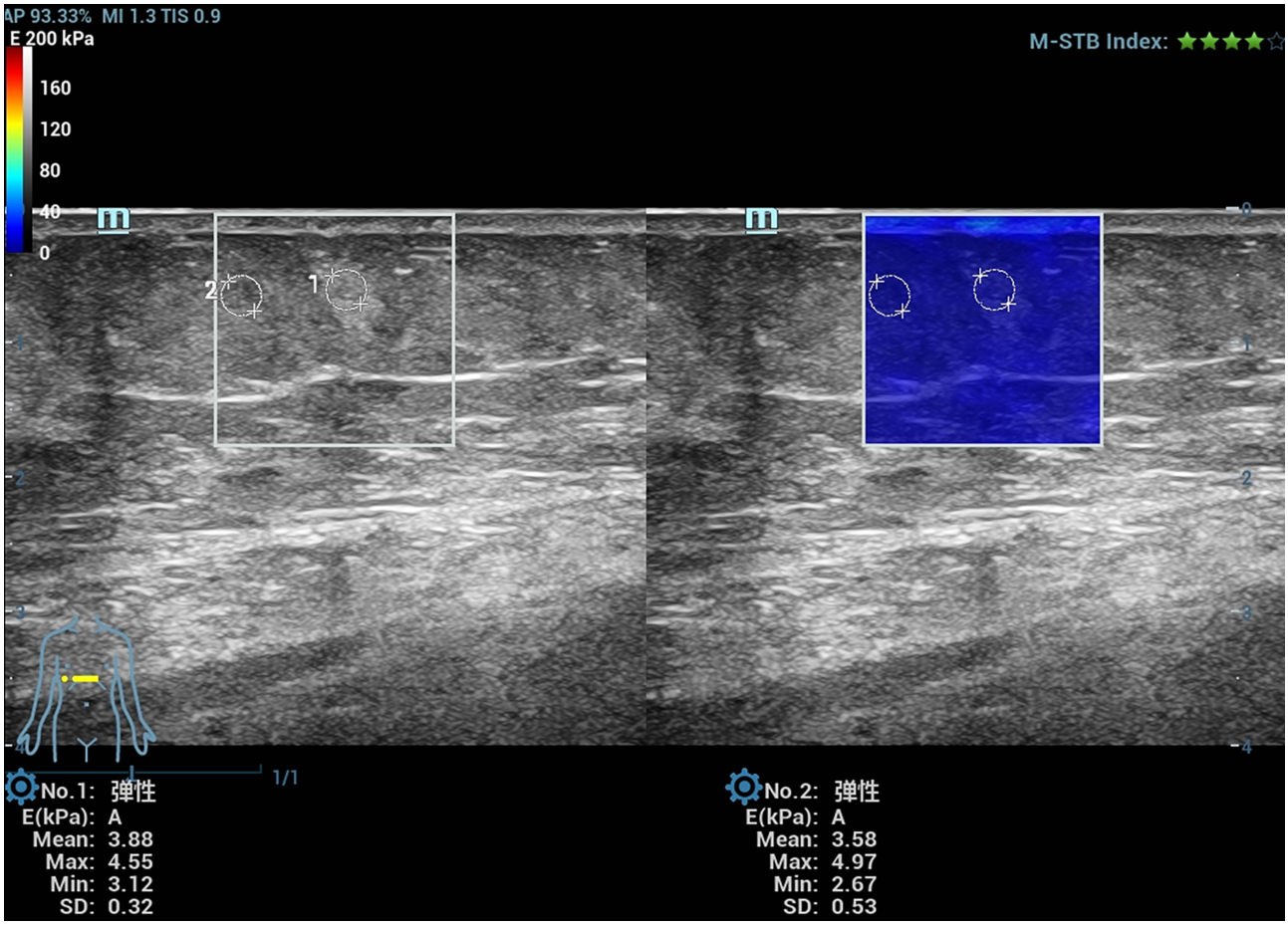

Figure 1 Representative STE examination image of the LH lesion and surrounding normal adipose tissue.
Note: Circle 1 is located over the LH lesion, and circle 2 is placed over the surrounding normal adipose tissue.

Quality Control

The collection of general clinical data and the ultrasound and STE examination findings for LH in all participants were conducted by two separate and dedicated teams, with each team being unaware of the other team's findings. The team performing the ultrasound and STE examinations of LH consisted of two certified attending physicians experienced in ultrasound assessment who conducted the examinations and documented the findings according to a standardized procedure and documentation protocol. In cases of disagreements in the results, a consensus was reached after consulting with a third senior attending physician with extensive ultrasound examination experience.

Statistical Analysis

All data analyses were performed using SPSS version 29.0. Normally distributed data were presented as $\overline{X} \pm S$, whereas non-normally distributed data were presented as M (Q1, Q3). The Wilcoxon signed-rank test was applied to compare Young's modulus values of the LH lesions and adjacent normal adipose tissue. Further, Spearman correlation analysis was used to explore associations between Young's modulus values of the LH lesions and the clinical characteristics. $P < 0.05$ was considered statistically significant.

Results

General Clinical Characteristics of the Participants

A total of 53 participants were included, of which 29 (54.7%) were male. The descriptive statistical results of the general clinical characteristics of all participants are presented in Table 1.

Routine Ultrasound Imaging Findings of the LH Lesions

All 53 participants were found to have LH lesions on ultrasound examination. The main characteristics of the ultrasound images of the LH lesions were as follows: 1. predominantly hyperechoic lesions were observed in 88.7% (47/53) of the participants; 2. color Doppler ultrasound examination primarily showed no significant blood flow signals in 94.3% (50/53) of the participants; 3. based on the presence or absence of clear boundaries, LH lesions were classified into three types, namely diffuse change, simple nodular change, and a mixed type with diffuse and nodular changes. In the participants of this study, simple nodular change was the predominant lesion type in 60.4% (32/53) of participants, followed by diffuse change in 3.8% (2/53) and mixed type in 35.8% (19/53).

Comparison of the STE-Derived Young's Modulus Values

The E_{max}, E_{mean}, and E_{min} values of the LH lesion group were 17.27 (12.01, 21.51) kPa, 10.58 (8.24, 15.98) kPa, and 7.07 (5.59, 9.16) kPa, respectively. Correspondingly, the surrounding normal adipose tissue group exhibited E_{max}, E_{mean}, and E_{min} values of 8.78 (6.78, 12.95) kPa, 6.29 (4.95, 8.42) kPa, and 4.49 (3.64, 5.29) kPa, respectively. The Wilcoxon signed-rank test revealed

Table 1 General Clinical Characteristics of the Participants

Clinical Characteristics	Total (n = 53)
Gender	
Male (n, [%])	29 (54.7%)
Female (n, [%])	24 (45.3%)
Age (years, $\overline{X} \pm S$)	61.87 ± 1.316
BMI (kg/m², $\overline{X} \pm S$)	22.49 ± 0.45
Diabetes duration (years, $\overline{X} \pm S$)	13.16 ± 1.16
HbA_{1c} level, (% $\overline{X} \pm S$)	8.89 ± 0.29
Daily insulin dose (U, $\overline{X} \pm S$)	23.21 ± 1.49
Daily injection frequency [times, M (Q1, Q3)]	2 (1.0, 3.5)
Dose per injection [U, M (Q1, Q3)]	9 (6.0, 14.0)
Duration of insulin injection (years, $\overline{X} \pm S$)	5.46 ± 0.73

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.

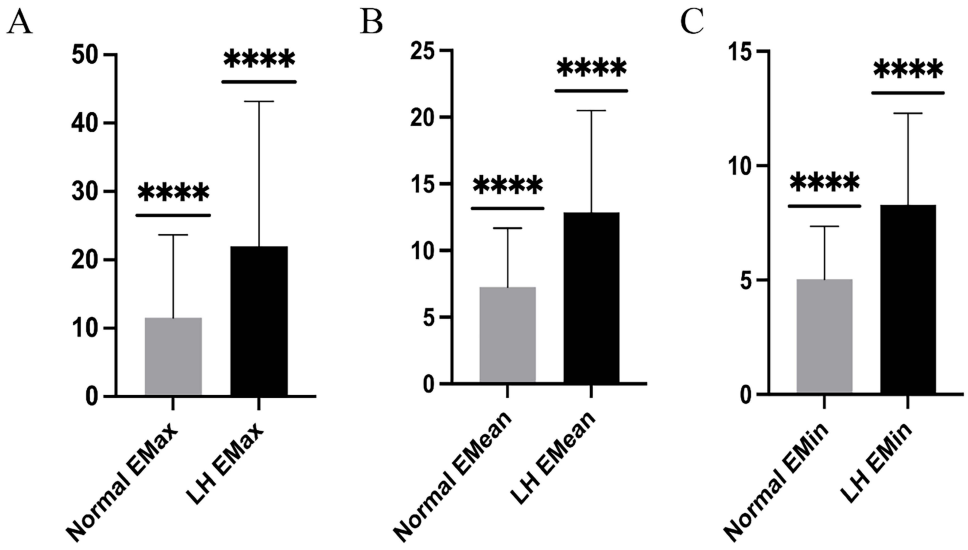

Figure 2 Comparison of Young's modulus values of the subcutaneous lipohypertrophy lesion and surrounding normal adipose tissue groups, (**A**) Comparison between normal E_{max} and LH_{max}. (**B**) Comparison between normal E_{mean} and LH_{mean}. (**C**) Comparison between normal E_{min} and LH_{min}.
Notes: LH represents the subcutaneous lipohypertrophy lesion group, and "normal" denotes the surrounding normal adipose tissue group. **** indicates $P < 0.001$.

significant differences between the LH lesion and the surrounding normal adipose tissue groups in terms of the E_{max} ($Z = -6.334$, $P < 0.001$), E_{mean} ($Z = -6.263$, $P < 0.001$), and E_{min} ($Z = -5.865$, $P < 0.001$) values (Figure 2A–C).

Correlation Between Young's Modulus Values of the LH Lesions and Clinical Features

The Spearman correlation method was employed to analyze the relationship between the observed clinical variables and Young's modulus elasticity values of the LH lesions. The analysis demonstrated a positive correlation between the E_{min} value of the LH lesions and HbA_{1c} levels ($P < 0.05$), but the correlation is weak (correlation coefficient [r] = 0.293). Apart from a slight correlation ($r = -0.005$) between the E_{max} value of the LH lesions and HbA_{1c} levels, no other notable or statistically significant correlations were observed between the other clinical variables and Young's modulus values of the LH lesions. The Spearman correlation analysis results are illustrated in Figure 3. In addition, the Mann–Whitney test revealed no significant differences between the different gender groups of the LH lesions in terms of the E_{max} ($U = 362.500$, $P > 0.05$), E_{mean} ($U = 324.000$, $P > 0.05$), and E_{min} ($U = 367.000$, $P > 0.05$) values.

Discussion

LH is the most frequent complication observed among individuals with diabetes mellitus undergoing insulin injection therapy.[14] LH functions as a critical pathological site that can markedly affect insulin absorption. Ultrasound examinations have a higher detection rate for LH than visual and tactile clinical examinations, as well as offer a more objective and accurate assessment.[7] In the current study, the ultrasound manifestations of LH primarily exhibited high echogenicity with clear boundaries, while color Doppler ultrasound did not demonstrate significant blood flow signals. A study by Johansson et al indicated that the high echogenicity found on the ultrasound examination of LH is related to tissue damage and fibrotic scarring caused by repeated subcutaneous injections[15] consistent with the results of our study.

Apart from the role of conventional ultrasound in screening for LH, Wang et al suggested that ultrasound can also provide additional information on the nature and severity of LH (including distribution and elasticity).[5] To date, there is a shortage of studies that have applied ultrasound elastography techniques to assess the hardness of LH lesions. This study is the first exploratory investigation of the application of ultrasound elastography-based STE imaging technology to assess the hardness of LH. The present study found significant differences in the STE-derived E_{max}, E_{mean}, and E_{min} values between the LH lesions and the surrounding normal adipose tissue. In particular, Young's modulus values of the LH lesions were higher than those of the surrounding normal adipose tissue, underlining the comparatively greater hardness of LH tissues. In a study by Zhao Henan et al, the hardness of lesions in breast invasive ductal carcinoma was

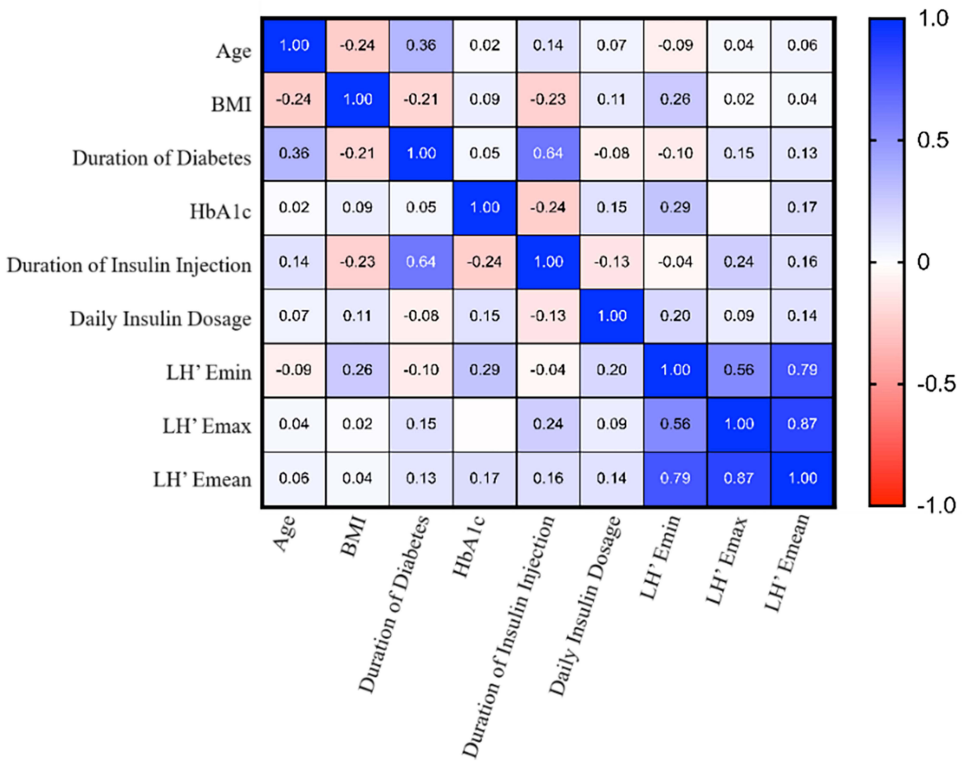

Figure 3 Correlation analysis results between Young's modulus values of the LH lesions and various clinical features.

reported to increase with higher histological grades. The researchers attributed this finding to the elevated tension in the lesion due to the extensive malignant proliferation of cancer cells and the concurrent increase in collagen fiber synthesis within the lesion.[16] The histological characteristics of LH lesions encompass enlarged and newly mitotic fat cells, accompanied by fibrosis and minor vascular changes.[5] However, the pathophysiological mechanism of LH has not yet been clarified. A study on the current progress of LH research indicated that most scholars consider LH occurrence to be related to the trauma of repeated injections caused by either the reuse of needles (eg, same needle usage more than five times) or failure to rotate the injection site.[17] Based on the elastic properties of the organs mentioned above and the histological characteristics of LH tissues, we propose that the increased hardness of LH lesions may be associated with a higher degree of internal fibrosis and the elevated lesion tension caused by enlarged fat cells and an increased number of newly formed fat cells. This potential relationship implies that greater fibrosis at the LH lesion site and more pronounced enlargement and/or increased proportion of newly formed fat cells can lead to a harder LH lesion. Consequently, relatively higher Young's modulus values will be obtained through STE imaging of LH lesions. This outcome supports the potential use of ultrasound elastography technology to assess internal characteristics such as the degree of fibrosis in LH lesions, providing additional quantitative measures for evaluating LH severity.

The present study also investigated the relationship between Young's modulus values of LH lesions and relevant clinical indicators such as HbA_{1c} levels. Our research revealed a unique finding of a positive correlation between the E_{min} values of LH lesions and HbA_{1c} levels and a minimal correlation between E_{max} values and HbA_{1c} levels. In STE imaging, the E_{min} and E_{max} values represent the minimum and maximum hardness in the area of interest, respectively. These results indicate that a higher hardness in the area of least hardness within an LH lesion correlates with higher HbA_{1c} levels in participants, with the area of minimum hardness being potentially related to insulin absorption. This observation further implies that more pronounced fibrosis or a greater abundance and enlargement of newly formed fat cells in the area of least hardness within an LH lesion could lower the efficiency of insulin absorption, thereby contributing to elevated blood sugar levels in the participants. Simultaneously, the lack of a notable correlation between E_{max} values and HbA_{1c} levels suggests that hardness alterations in the area of maximum hardness within an LH lesion are

not linked to the rate of insulin absorption. An investigation by Xu et al reported that the fibrosis of fat cells induced by long-term injections at the same site could lead to delayed and unpredictable insulin release, ultimately diminishing insulin bioavailability.[18] The authors postulate that an increase in the degree of fibrosis or tension within an LH lesion site above a certain threshold establishes that site as the area of maximum hardness within the lesion and the smallest number of normal fat cells. Consequently, the level of insulin absorption at this site may be extremely low or nearly non-existent. Furthermore, this finding indicates that the changes in the E_{max} value within an LH lesion may be completely unrelated to the alterations in insulin absorption levels, resulting in the lack of a noteworthy correlation between the E_{max} value of the LH lesion and HbA_{1c} levels. Previous research has mostly focused on the overall relationship between LH and fluctuations in the blood sugar levels of participants. In contrast, this study delved deeper into the different compositional areas within individual LH lesions and explored their correlation with HbA_{1c} levels, suggesting that the STE-derived E_{min} values have certain applicability in assessing the severity of individual LH lesions. Additionally, our study findings offer preliminary imaging data supporting future basic research on insulin absorption conditions across different compositional areas within LH sites.

Limitation

This study has a few limitations that should be considered. The small sample size in this study necessitates further research with larger cohorts to confirm the correlations between Young's modulus elasticity values of LH lesions and HbA_{1c} levels, thus validating the conclusions of our study. This study strictly enforced the exclusion criteria, which may limit the generalization of the results. Moreover, this research utilized ultrasound elastography technology-based STE to assess the hardness of LH lesions and hypothesized a correlation of the degree of fibrosis with the number of newly formed fat cells and fat cell enlargement. However, we did not conduct biopsy sampling of the LH tissue for histological examination, thus lacking a gold standard for pathological analysis. Therefore, the hypotheses of this study can be validated by conducting future studies incorporating animal-based experimental investigations to gain insight into the relationship between the histological components of LH tissue and its elasticity/hardness values.

Conclusion

In summary, this study employed STE to assess the hardness of LH lesions, providing the first quantitative ultrasound elastography technology-based evidence that indicated that LH lesions are harder than surrounding normal adipose tissue. Furthermore, our results revealed that the E_{min} values of LH lesions are positively correlated with HbA_{1c} levels. This research expands the available multimodal imaging approaches for evaluating LH lesions as well as adds to the exploratory findings supporting the feasibility of ultrasound elastography in measuring the hardness and severity of abdominal LH lesions among individuals undergoing insulin injection therapy for type 2 diabetes.

Data Sharing Statement

The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The present study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Affiliated People's Hospital of Ningbo University (Approval No. 2023-SR-076), with all participants providing written informed consent.

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Disclosure

The authors report no conflict of interest.

References

1. International Diabetes Federation. IDF diabetes atlas. Available from: http://www.Diabetesatlas.org. Accessed November 22, 2024.
2. Deeb A, Abdelrahman L, Tomy M, et al. Impact of insulin injection and infusion routines on lipohypertrophy and glycemic control in children and adults with diabetes. *Diabetes Ther*. 2019;10(1):259–267. doi:10.1007/s13300-018-0561-7
3. Ji L, Sun Z, Li Q, et al. Lipohypertrophy in China: Prevalence, risk factors, insulin consumption, and clinical impact. *Diabetes Technol Ther*. 2017;19(1):61–67. doi:10.1089/dia.2016.0334
4. Wang K, Zhang S, Liu C, Chen Y. A meta-analysis and meta-regression on the prevalence of lipohypertrophy in diabetic patients on insulin therapy. *Therapie*. 2021;76(6):617–628. doi:10.1016/j.therap.2021.04.002
5. 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*. 2021;100(29):e26743. doi:10.1097/MD.0000000000026743
6. Wang Hong YJ, Meijing Z. Study on the correlation between subcutaneous lipohyperplasia due to insulin injection in patients with Type 1 diabetes and multidimensional blood glucose fluctuations. *Chin J Endocrinol Metab*. 2023;3:236–241.
7. Chen Liming GL. Interpretation of the "Chinese expert consensus on the prevention and treatment of subcutaneous lipohyperplasia related to insulin injection. *China Med Frontiers J*. 2022;04:7–9.
8. Kapeluto JE, Paty BW, Chang SD, Meneilly GS. Ultrasound detection of insulin-induced lipohypertrophy in Type 1 and Type 2 diabetes. *Diabet Med*. 2018;35(10):1383–1390. doi:10.1111/dme.13764
9. Shi Yun YJ, Hong W, Min Z, et al. The effect of the depth of subcutaneous lipohyperplasia under insulin injection on blood glucose control in diabetic patients. *Chin J Endocrinol Metab*. 2021;27(11):1001–1003.
10. Zheng Jian WM, Min Z. Study on the repeatability of liver and spleen stiffness measurement by acoustic radiation force impulse imaging and shear wave el astography. *Chin J Hepatic Surg*. 2019;04, 366–369.
11. Zhang L, Xu J, Wu H, et al. Screening breast lesions using shear modulus and Its 1-mm shell in sound touch elastography. *Ultrasound Med Biol*. 2019;45(3):710–719. doi:10.1016/j.ultrasmedbio.2018.11.013
12. Huang J, Yeung AM, Kerr D, et al. Lipohypertrophy and insulin: an old dog that needs new tricks. *Endocr Pract*. 2023;29(8):670–677. doi:10.1016/j.eprac.2023.04.006
13. Bertuzzi F, Meneghini E, Bruschi E, Luzi L, Nichelatti M, Epis O. Ultrasound characterization of insulin induced lipohypertrophy in type 1 diabetes mellitus. *J Endocrinol Invest*. 2017;40(10):1107–1113. doi:10.1007/s40618-017-0675-1
14. Abu Ghazaleh H, Hashem R, Forbes A, et al. A systematic review of ultrasound-detected lipohypertrophy in insulin-exposed people with diabetes. *Diabetes Ther*. 2018;9(5):1741–1756. doi:10.1007/s13300-018-0472-7
15. Johansson UB, Amsberg S, Hannerz L, et al. Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care*. 2005;28(8):2025–2027. doi:10.2337/diacare.28.8.2025
16. Zhao Henan LZ, Weidong Y. Application study of shear wave elastography and superb microvascular imaging in the pathological grading of invasive ductal carcinoma of the breast. *Chin J Ultrason Imaging*. 2017; 02:146–150.
17. Zhang Q, Jia P, Wang L. Research progress on insulin-induced lipohypertrophy. *Chin J Modern Nurs*. 2023;2023:1.
18. Xu X-H, Carvalho V, Wang X-H, Qiu S-H, Sun Z-L. Lipohypertrophy: prevalence, clinical consequence, and pathogenesis. *Chin Med J*. 2021;134(1):47–49. doi:10.1097/CM9.0000000000000970