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Exploratory study on glycemic control improvement for patients with diabetes mellitus by appropriate re-education on insulin self-injection technique during COVID-19 pandemic

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A R T I C L E  I N F O
Keywords:
Diabetes mellitus
Insulin treatment
Self-injection technique
Re-education
COVID-19 pandemic

A B S T R A C T

Aims: To conduct a study on glycemic control improvement by appropriate re-education on the self-injection technique (SIT) in patients with diabetes mellitus undergoing insulin therapy.

Methods: Patients who received appropriate SIT and were treated with insulin for more than a year were re-educated. For the observation period of six months, the subjects’ SIT was checked, and hemoglobin A1c (HbA1c) levels were measured at each visit. HbA1c levels, insulin doses, and behavioral changes in SIT were investigated at baseline and at the end of the observation period.

Results: In the per-protocol set population, the HbA1c level decreased by 0.2 % (2.0 mmol/mol) on average, showing a significant difference (p = 0.009). No significant difference was observed in the proportion of subjects with decreased HbA1c levels, changes in total daily insulin doses, or blood glucose levels. Four of the six SIT items covered by re-education were improved.

Conclusions: Providing re-education on insulin SIT was considered effective in reducing HbA1c levels and improving adherence to proper SIT.

1. Introduction

The number of patients with diabetes mellitus is increasing worldwide [1]. Although many therapeutics, including oral drugs, have become available [2–6], insulin therapy is reportedly used by 7.4 % of patients with Type 2 diabetes mellitus (equivalent to 34 million people based on the number of patients in 2019 [1]) in addition to patients with Type 1 diabetes mellitus, for whom insulin therapy is essential [7]. Thus, insulin therapy remains one of the mainstays of drug therapy for diabetes.

In insulin therapy, adherence to the self-injection technique (SIT) learned at the time of therapy initiation is important. In clinical practice, however, we often encounter cases in which patients who initially carefully followed the precautions started deviating from the proper SIT, resulting in poor outcomes. For example, repeated insulin injections in the same location may cause lesions such as abnormally swollen or hard adipose tissue underneath the surface of the skin, known as lipohypertrophy (LH) [8,9]. Some patients may intentionally repeat injections into the LH because it is less painful. However, injection into LH has been reported to adversely affect glycemic control due to decreased insulin absorption [10–12]. Rotation of the injection site is an important SIT element that prevents LH development [13]. As described so far, SIT is considered one of the factors influencing glycemic control, and improvement in glycemic control has been reported to be expected through re-education focusing on SIT [14–19]. It is important to verify such findings in countries with diverse racial groups and healthcare systems. However, in Japan, only a few studies have investigated the relationship between re-education on insulin SIT and glycemic control [20,21]. Thus, we conducted this study to further investigate this relationship by assessing the level of hemoglobin A1c (HbA1c) as a marker

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https://doi.org/10.1016/j.diabres.2022.110192
Received 18 August 2022; Received in revised form 15 November 2022; Accepted 23 November 2022
Available online 28 November 2022
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for improvement in glycemic control and observed behavioral changes in SIT brought about by appropriate SIT re-education. This study just happened to be conducted in the midst of the global COVID-19 pandemic, providing an opportunity to study this important consideration in such unusual healthcare environments.

2. Subjects and methods

2.1. Subjects and study design

In accordance with the protocol, the study included outpatients with diabetes mellitus who met all the inclusion criteria and none of the exclusion criteria. The inclusion criteria were as follows: (1) outpatients with diabetes mellitus aged 20 years or older; (2) patients with a history of insulin self-injection for at least one year; (3) patients with no history of hospitalization within six months prior to study enrollment; (4) patients who self-injected insulin at least three times daily; (5) patients who were using or going to be prescribed BD MicroFine Pro 32G × 4 mm pen needles (Nippon Becton Dickinson Company, Ltd., Tokyo, Japan) for insulin self-injection; (6) patients who could understand the content of SIT education and correctly perform the SIT; and (7) patients who could understand all aspects of the study and voluntarily gave written informed consent. The exclusion criteria were as follows: (1) patients who were and might be pregnant; (2) patients receiving steroid therapy with a dose change during the treatment course; (3) patients undergoing treatment for active malignancy; (4) patients deemed ineligible for study participation by a physician; and (5) patients who did not consent to study participation or voluntarily withdrew from the study prior to study completion.

Before the start of observation, the HbA1c level, total daily insulin dose, blood glucose level, and daily SIT were examined, and the presence/absence and number of LH at the injection sites (upper arms, thighs, buttocks, and abdomen) were checked visually and by palpation [22]. Patients who received appropriate SIT and were treated with insulin for more than a year were re-educated. Specifically, a certified nurse in diabetes care and education conducted SIT re-education using standardized and printed educational materials on the following six elements: “air shot before injection,” “pinching up of the skin,” “injection angle (vertical or diagonal),” “site rotation,” “holding 10 counts after injection,” and “do not reuse pen needles.” Furthermore, the subjects’ SIT was checked at each visit during the observation period, and re-education was repeatedly provided as needed. A BD MicroFine Pro 32G × 4 mm was uniformly used as the injection needle in this study. After completion of the observation period of six months, we recorded the changes in HbA1c levels from baseline, the proportion of subjects with decreased HbA1c levels, and percentage change in HbA1c levels, as well as changes in total daily insulin doses from baseline, blood glucose levels, and SIT behaviors. Reeducation on insulin SIT was conducted based on the recommendations of the Forum for Injection Technique and Therapy: Expert Recommendations (FITTER) [13].

2.2. Statistical analysis

Demographics, baseline characteristics of the subjects, and other general study data were summarized using descriptive statistics. Summary statistics included the mean and standard deviation for continuous variables, and frequency counts and percentages for categorical variables. For inferential analysis, we used the paired samples t-test for changes in HbA1c levels, blood glucose levels, and total daily insulin doses; the binomial test for the proportion of subjects with improved HbA1c levels; the one-sample t-test for the percentage change in HbA1c levels; and the exact binomial or multinomial test of goodness-of-fit for behavioral changes in SIT. SAS software (version 9.4; SAS Institute Inc., NC) was used for the analysis. A p-value < 0.05 was considered statistically significant.

2.3. Study registration and ethics

This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee at Medical Research Institute KITANO HOSPITAL, PIIF Tazuke-Kofukai (Approval No.: P190901000). The study protocol was registered with the University Hospital Medical Information Network Center Clinical Trials Registry (UMIN-CTR) (UMIN000037845). All participants provided written informed consent to participate in the study.

3. Results

3.1. Background

A total of 120 subjects were enrolled in the study between March and August 2020, and the observation of the last subject was completed in April 2021. Due to insufficient or missing observational data, six subjects were excluded from the analysis, leaving 114 subjects included in the intention-to-treat (ITT) population. Additionally, owing to insufficient observational data concerning the primary endpoint and protocol violation, 21 subjects were excluded, leaving 93 subjects included in the per protocol set (PPS) population. The baseline characteristics of the participants are presented in Table 1. The ITT population comprised 68 males and 46 females, including 49 subjects with type 1 diabetes mellitus, 57 with type 2 diabetes mellitus, and 8 with other types of diabetes. The PPS population comprised 53 men and 40 women, including 42 subjects with type 1 diabetes mellitus, 46 with type 2 diabetes mellitus, and 5 with other types of diabetes. The mean and standard deviation of age, duration of insulin therapy, HbA1c level, and blood glucose level were 64.2 ± 14.0 years, 13.9 ± 9.9 years, 7.9 ± 1.1 % (62 ± 12 mmol/mol), and 160.4 ± 79.6 mg/dL in the ITT population, and 63.8 ± 14.8 years, 14.4 ± 10.5 years, 7.8 ± 1.0 % (61 ± 10 mmol/mol), and 153.0 ± 51.9 mg/dL in the PPS population, respectively. The most commonly used pen needles before study initiation were BD MicroFine Plus 32G × 4 mm (Nippon Becton Dickinson Company, Ltd., Tokyo, Japan) and NovoFine® Plus 32G × 4 mm (Novo Nordisk Pharma Ltd., Tokyo, Japan); the former was used by 60 and 51 subjects in the ITT and PPS populations, respectively, and the latter was used by 52 and 40 subjects in the ITT and PPS populations, respectively.

Table 1

| Demographics and baseline characteristics of subjects. | ITT population | PPS population |
|-------------------------------------------------------|----------------|---------------|
| Number of subjects                                    | 114            | 93            |
| Male/female                                           | 68/46          | 53/40         |
| Age, years                                            | 64.2 ± 14.0    | 63.8 ± 14.8   |
| Duration of diabetes, years                           | 20.3 ± 11.1    | 20.6 ± 11.3   |
| Duration of insulin treatment, years                  | 13.9 ± 9.9     | 14.4 ± 10.5   |
| Type of diabetes, Type 1/Type 2/ others               | 49/57/8        | 42/46/5       |
| HbA1c, % (mmol/mol)                                   | 7.9 ± 1.1 (62 ± 12) | 7.8 ± 1.0 (61 ± 10) |
| Blood glucose level, mg/dL                           | 160.4 ± 79.6   | 153.0 ± 51.9  |
| Number of insulin injection per day                   | 3.8 ± 0.4      | 3.8 ± 0.4     |
| Total daily insulin dose, unit                        | 35.4 ± 19.8    | 33.0 ± 14.9   |
| Site of insulin self-injection                        | Upper arm †    | 10 (8.8)      | 8 (8.6)       |
|                                                      | Thigh †        | 13 (11.4)     | 9 (9.7)       |
|                                                      | Buttock †      | 2 (1.8)       | 2 (2.2)       |
|                                                      | Abdomen †      | 114 (100.0)   | 93 (100.0)    |
| Number of subjects with lipohypertrophy              | 51 (1.9 ± 0.5) | 41 (1.9 ± 0.5) |
| Visual inspection ‡                                    | 69 (2.2 ± 1.0) | 54 (2.1 ± 1.0) |

* Number of subjects based on multiple choice (%) at each injection site. ‡ Number of subjects with lipohypertrophy (number of lipohypertrophy, Mean ± SD). HbA1c; Hemoglobin A1c; ITT, intent to treat; PPS, per protocol set.
3.2. Changes in glycemic control

Due to the missing data noted at the completion of the observation period, 21 of the 114 subjects in the ITT population were excluded from the analysis, leaving 93 subjects included in the ITT population, which is the same as the number of subjects in the PPS population. Therefore, the results are shown only for the PPS population in this study, and the results, including the ITT population, are presented in Supplementary Table 1. The mean and standard deviation of the HbA1c level decreased by 0.2 % (2.0 mmol/mol) from 7.8 ± 1.0 % (61 ± 10 mmol/mol) at baseline to 7.6 ± 0.8 % (59 ± 8.5 mmol/mol) at the end of the observation period \((p = 0.009)\), and the percentage change in the HbA1c level over the same period was \(-1.9 \% (-2.4 \text{ mmol/mol}) (p = 0.027)\), both showing statistically significant differences. On the other hand, no statistically significant changes were observed in blood glucose levels, the proportion of subjects with improved HbA1c levels, or the total daily insulin dose (Table 2).

3.3. Behavioral changes in SIT

Due to the missing data noted at the completion of the observation period, 20 of the 114 subjects in the ITT population were excluded from the analysis, leaving 94 subjects included in the ITT population. Since the results of the statistical analysis were similar to those of the PPS population, the results are shown only for the PPS population in this text; the results, including the ITT population, are presented in Supplementary Table 2. Regarding SIT behaviors, a statistically significant improvement was observed in four of the six items in both populations. Statistically significant improvement was observed in subjects who “do not pinch up the skin at all” from 61.3 \% (57/93) to 69.9 \% (65/93) \((p = 0.009)\); subjects who “rotate the injection site each time” from 81.7 \% (76/93) to 93.5 \% (87/93) \((p < 0.001)\); subjects who “hold 10 counts after each injection” from 63.4 \% (59/93) to 97.8 \% (91/93) \((p < 0.001)\); and subjects who “do not reuse pen needles at all” from 90.3 \% (84/93) to 94.6 \% (88/93) \((p = 0.005)\) (Table 3).

3.4. Lipohypertrophy

The number of subjects with LH confirmed visually and by palpation at baseline were 51 and 69 in the ITT population and 41 and 54 in the PPS population, respectively (Table 1). In the ITT population, the number of LH confirmed by palpation was approximately 52 \% higher than that confirmed by visual inspection alone, and nearly 95 \% of LH was located in the abdomen (Table 4).

4. Discussion

We conducted an observational study on glycemic control improvement by appropriate re-education on insulin SIT in outpatients with diabetes mellitus at a single institution in Japan. At the end of the observation period of six months in subjects in both the ITT and PPS populations, the HbA1c levels decreased by 0.2 \% (2.0 mmol/mol) \((p = 0.009)\), with a decrease in the percentage change of 1.9 \% (2.4 mmol/mol) \((p = 0.027)\), thereby indicating statistically significant improvement. However, the decrease was small and no statistically significant difference was observed in the proportion of subjects with decreased HbA1c levels, changes in total daily insulin doses, or changes in blood glucose levels. In a randomized controlled trial reported by Misnikova et al., HbA1c levels decreased by 1.0 \% over six months after the provision of SIT education [15], Chen et al. also found a 0.31 \% (3.4 mmol/mol) difference in the HbA1c levels in the PPS population after SIT re-education compared to that of the control population who received no SIT re-education \((p = 0.038)\). The reduction in the total daily insulin dose was reported to be \(-8\) units in the PPS population after insulin SIT re-education, indicating a substantial decrease compared to the control population without SIT re-education \((-1\) unit) [16]. In these studies, the baseline HbA1c levels were 8.7 ± 1.4 \% (72 mmol/mol) and 8.6 ± 1.0 \% (71 ± 10.9 mmol/mol), respectively [15,16], which were much higher than those observed in the present study. In the exploratory analysis performed after the completion of the present study, the subjects in the PPS population were divided into a group with HbA1c < 8.0 \% (N = 57) and a group with HbA1c ≥ 8.0 \% (N = 36). The difference in the HbA1c level in each group was \(+0.02 \% (0.2 \text{ mmol/mol}) (p = 0.763)\) and \(-0.51 \% (-5.6 \text{ mmol/mol}) (p < 0.001)\), respectively. Since a statistically significant improvement was observed in the group with HbA1c ≥ 8.0 \% (Supplementary Table 3), the effects of SIT education were presumed to be expressed more clearly in patients with high HbA1c levels, which is in line with the published literature.

Regarding behavioral changes in SIT from baseline to the end of the observation period, subjects in both the ITT and PPS populations showed statistically significant improvement in the proportions of subjects who “do not pinch up the skin at all,” “rotate the injection site each time,” “hold 10 counts after each injection,” and “do not reuse pen needles at all.” On the other hand, the rates of adherence to “air shot before injection” and “injection angle (vertical or diagonal)” were already high.
before the start of the study, thus resulting in no statistically significant improvement in these techniques. Despite the fact that some of the subjects claimed prior to the start of the observation period that they had rotated the injection site every time, they had been doing it improperly, in such a way as to rotate the injection site only within a small area of the abdomen or simply switch from one side of the abdomen to the other (with the umbilicus as a center). The use of illustrations was considered useful to obtain specific information on how to rotate the injection sites and to provide the correct information regarding proper site rotation. For the optimization of the SIT, the characteristics of the insulin pen needle are also important. The shorter needle and flat hub are expected to help expand the area of injection site rotation by reducing pain and increasing ease of injection. In this study, most of the patients had previously used 32G × 4 mm pen needles, and nearly half of the patients had used flat-hub needles. As there were no differences in the characteristics of the needles used before and after device switching, evaluations based on differences in needle length or shape were not possible. However, it was considered that these needle characteristics may have played a part in the significant improvement in SIT brought about by re-education.

Although LH was identified frequently in our study, the frequency of LH detection varies among studies [23]. The method of identifying LH requires a certain level of accuracy [22], and the observation period of 6 months in this study is considered too short to verify the changes in LH brought about by re-education. There are detailed studies demonstrating improvements in LH and glycemic control [17,18]. The continuous management of LH has been shown to contribute to risk reduction and improved cost-effectiveness during insulin treatment [19]. The number of LH confirmed by palpation was approximately 52% higher than that confirmed by visual inspection alone, indicating that palpation is more effective than visual inspection in detecting LH.

This study is notable in that it was conducted during the time when COVID-19 was spreading worldwide, including in Japan. In Osaka, where the study site was located, restrictions were imposed on outings by the state of emergency declaration, which posed concerns regarding its impact on patients’ glycemic control. For example, while the worsening of patients’ glycemic control was attributed to lack of exercise and increased frequency of snack consumption resulting from not being able to go out, improvement in glycemic control was also expected due to reduced opportunities to eat or drink outside the home. In the systematic review reported by Eberle et al. on glycemic control in patients with diabetes under lockdown, HbA1c levels decreased by 0.05% (95% CI: −0.31–0.21) in patients with type 1 diabetes mellitus and increased by 0.14 (95% CI: −0.13–0.40) in patients with type 2 diabetes mellitus [24], and the impact of the restriction on glycemic control was not enormous on average. As with this study, several observational studies have been reported in Japan during the COVID-19 pandemic. Masuda et al. reported a significant decrease in HbA1c levels [25], while Hosomi et al. reported a significant increase in HbA1c levels [26]. Thus, the impact of the COVID-19 pandemic on HbA1c levels varied depending on the patients’ individual activities of daily living or lifestyle. Although group education and in-person medical care were often avoided during the pandemic, we believe that this study was able to show patient acceptance and the usefulness of individual guidance conducted with sufficient precautions to prevent contact with the infection.

This study had some limitations. First, as an observational study, a randomized controlled trial should be performed to confirm clear and consistent improvement in HbA1c levels. Second, the study was conducted at a single center in one city, and further investigation involving multiple centers is required. Third, patients with Type 1 and Type 2 diabetes mellitus were not distinguished in our investigation. Regardless of the type of diabetes mellitus, all the patients were self-injected with insulin at least three times daily. No major differences in injection doses and locations were observed between the two types; therefore, we considered them as one group for our analysis. However, this needs to be further examined as the number of subjects in this study was limited. Finally, since the exploratory analysis suggested that improved glycemic control may be expected in patients with HbA1c ≥ 8.0%, further investigation in patients with high HbA1c levels is necessary.

This study suggested that providing continuous SIT re-education in daily clinical practice was effective for adherence to proper SIT and potential improvement of glycemic control.

**Authorship contribution statement**

SH, YK (Koshii), ST, HT, and AH contributed to study protocol development, data analysis, and manuscript writing. SH, YK (Koshii), YK (Keidai), YS, YI, KI, SA, and AH performed the study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, had full access to all of the study data, and take complete responsibility for the integrity of the data, the accuracy of the data analysis, and integrity of the work as a whole, and gave final approval for the version to be published.

**Declaration of Competing Interest**

ST and HT are employees of Nippon Becton Dickinson Company Ltd. The other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

**Acknowledgements**

We thank Dr. Shailendra Bajpai, Becton Dickinson Holdings Pte Ltd., and Dr. Yoriko Kato, Nippon Becton Dickinson Company, Ltd., for their input on the content of this manuscript and editorial assistance.

**Funding**

This study was funded by Nippon Becton Dickinson Company, Ltd.

**Appendix A. Supplementary material**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110192.

**References**

[1] International Diabetes Federation [Internet]. Brussels, Belgium 2021. IDF Diabetes Atlas - 10th Edn. [cited 2022 Feb 2]. Available from: https://diabetesatlas.org/.

[2] Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care 2016;39(Suppl 2):S137–45. https://doi.org/10.2337/dc15-3007.

[3] Abdul-Ghani MA, Puckett C, Triplitt C, Maggs D, Adams J, Cerinomso E, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDITC): a randomized trial. Diabetes Obes Metab 2015;17(3):268–75.

[4] Matthews DR, Paldanini PM, Proor P, Chiang Y, Stumvoll M, Prato SD, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERITY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394(10208):1519–29. https://doi.org/10.1016/S0140-6736(19)32131-2.

[5] Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;155(9):602.

[6] Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. Clin Pharmacol Ther 2019;105(5):1213–23. https://doi.org/10.1002/cpt.1397.

[7] Baro S, Yafkin JS, Kehlenbrink S, Davies J, Wild SH, Lipka KJ, et al. Estimation of global insulin use for type 2 diabetes, 2018–2030: a metaanalysis simulation. Lancet Diabetes Endocrinol 2019;7(1):25–33. https://doi.org/10.1016/S2213-8587(18)30303-6.

[8] Nilsson MR. Insulin amyloid at injection sites of patients with diabetes. Amyloid 2016;23(3):199–47. https://doi.org/10.1080/15309249.2016.1179183.

[9] Gentile S, Guarino G, Corte TD, Marino G, Fusco A, Corigliano G, et al. Insulin-induced Skin lipohypertrophy in Type 2 Diabetes: a Multicenter Regional Survey in Southern Italy. Diabetes Ther 2020;11(9):2001–17.
Famulla S, Hovelmann U, Fischer A, Coester H-V, Hermanski L, Kalthoeuer M, 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):1486–92.

Frid AH, Hirsch LJ, Menchior AR, Morel DR, Strauss KW. Worldwide Injection Technique Questionnaire Study: Injecting Complications and the Role of the Professional. Mayo Clin Proc 2016;91(9):1224–30. https://doi.org/10.1016/j.mayocp.2016.06.012.

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):445–53. https://doi.org/10.1016/j.diabet.2013.05.006.

Grassi G, Scuntero P, Trepiccioni R, Marubbi F, Strauss K. Optimizing insulin injection technique and its effect on blood glucose control. J Clin Transl Endocrinol 2014;1(4):145–50. https://doi.org/10.1016/j.jcte.2014.07.006.

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(6):1309–18. https://doi.org/10.1007/s13300-017-0315-y.

Chen L, Xing Q, Li J, Zhou J, Yuan Yi, Wan Y, et al. Injection Technique Education in Patients with Diabetes Injecting Insulin into Areas of Lipohypertrophy: A Randomized Controlled Trial. Diabetes Ther 2021;12(3):813–26.

Gentile S, Guarino G, Della Corte T, Marino G, Satta E, Pasquarella M, 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):1379–98.

Gentile S, Guarino G, Della Corte T, Marino G, Satta E, Pasquarella M, et al. The Durability of an Intensive, Structured Education-Based Rehabilitation Protocol for Best Insulin Injection Practice: The ISTERP-2 Study. Diabetes Ther 2021;12(9):2557–69.

Gentile S, Guarino G, Della Corte T, Marino G, Satta E, Pasquarella M, et al. The Economic Burden of Insulin Injection-Induced Lipohypertrophy. Role of Education: The ISTERP-3 Study. Adv Ther 2022;39(5):2192–207.

Nakatani Y, Matsunawa M, Monden T, Aso Y, Nakamoto T. Improvement of Glycemic Control by Re-education in Insulin Injection Technique in Patients with Diabetes Mellitus. Adv Ther 2013;30(10):897–906. https://doi.org/10.1007/s12225-013-0066-8.

Omori K, Kawamura T, Urata M, Matsunawa M, Kazama M, Imamine R, et al. Effect of re-coaching on self-injection of insulin in older diabetic patients - Impact of cognitive impairment. Diabetes Res Clin Pract 2017;130:34–42.

Gentile S, Guarino G, Giancaterini A, Guida P, Strollo F. AMD-OSDI Italian Injection Technique Study Group. A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. Springerplus 2016;5:563. https://doi.org/10.1186/s40064-016-1978-y.

Deng N, Zhang X, Zhao F, Wang Y, He H. Prevalence of lipohypertrophy in insulin-treated diabetes patients: A systematic review and meta-analysis. J Diabetes Investig 2017;9(3):536–43. https://doi.org/10.1111/jdi.12742.

Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: a systematic review. Diabetol Metab Syndr 2021;13(1):95. https://doi.org/10.1186/s13098-021-00705-9.

Masuda M, Tomonaga O. Study on the effects of changes in lifestyle of patients with diabetes on glycemic control before and after the declaration of the state of emergency in Japan. Diabetol Int 2021;13(1):1–9. https://doi.org/10.1007/s13340-021-00505-4.

Hosomi Y, Munekawa C, Hashimoto Y, Okamura T, Takahashi F, Kawano R, et al. The effect of COVID-19 pandemic on the lifestyle and glycemic control in patients with type 1 diabetes: a retrospective cohort study. Diabetol Int 2022;13(1):85–90.