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RESEARCH ARTICLE

Ameliorating Insulin Injection Site Rotation and its Impact on Lipohypertrophy Incidence and Glycemic Control in Patients with Diabetes

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Abstract:

Background:

This study aimed to evaluate the effect of ameliorated insulin injection site rotation on the incidence of Lipohypertrophy (LH) and glycemic control in patients with diabetes.

Methods:

A quasi-experimental design involving a pretest-posttest with a control group was utilized at the medical outpatients' clinic of Sohag University Hospital. The participants were divided into two groups (30 in the study group and 30 in the control group). Two instruments were utilized to collect the data, *i.e.*, a sociodemographic and clinical data sheet and a lipohypertrophy assessment sheet.

Results:

The majority have been found to suffer from type I DM with an insulin injection duration from one to less than 6 months. A significant reduction has been noticed in the lipohypertrophy incidence and grade during the 6-month assessment compared to the pre-intervention assessment.

Conclusion:

A marked reduction in the incidence of LH and improved glycemic control have been noted in the study group, indicating the clinical significance of the anti-clockwise insulin site rotation technique.

Keywords: Insulin injection, Site rotation, Lipohypertrophy, Glycemic control, Diabetes, TID.

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1. INTRODUCTION

Diabetes mellitus poses a significant and expanding global health challenge, characterized by its chronic nature [1]. In recent years, there has been a notable increase in diabetes cases worldwide, attributed to factors, such as aging populations, rapid economic growth, and changes in lifestyles [2]. While there have been considerable strides in managing Type 1 Diabetes (T1D), particularly with intensive insulin treatments, challenges still remain. Intensive insulin therapy is crucial for achieving better blood sugar control and reducing long-term complications in both type 1 and long-standing type 2 diabetes. However, despite its benefits, there are still barriers to overcome. One such obstacle is the occurrence of skin complications, which are increasingly reported and can impede efforts to achieve optimal blood sugar levels. Lipodystrophy, a common skin reaction in diabetic patients undergoing insulin therapy, is among these complications [3].

Despite lipodystrophy being a common occurrence, there are challenges in effectively advising patients with type 1 diabetes and their caregivers on how to avoid it. Lipodystrophy, the most prevalent skin issue, affects the fat tissue under the skin and can be categorized into two types: lipohypertrophy and lipoatrophy, each with its own causes and prevalence rates [3]. Lipohypertrophy, more frequent than

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lipoatrophy, involves the buildup of fat tissue at insulin injection sites, leading to lumps, thickened areas, and firmness under the skin due to repeated insulin injections [4]. Histological analysis shows that adipocytes, or fat cells, exhibit enlarged sizes and contain numerous lipid droplets. Although the exact mechanisms behind this condition are not fully understood, it is hypothesized that repetitive mechanical trauma from needle insertion and the local effects of insulin may contribute to the excessive growth of fat tissue in affected areas.

Lipoatrophy manifests as visible depressions in the skin at sites where subcutaneous insulin is administered. The exact cause is not fully understood, but it is speculated to involve immune-mediated damage, potentially linked to elevated insulin antibody levels and other autoimmune conditions, like coeliac disease and Hashimoto thyroiditis. Repetitive mechanical trauma, cryoinjury, and abscess formation are also considered possible factors. Histologically, lipoatrophy is characterized by significant infiltration of mast cells. Lipodystrophy in these areas may impede insulin absorption, leading to fluctuations in blood glucose levels and glycemic control [5].

Failure to rotate insulin injection sites properly can lead to the development of lipohypertrophy, which significantly impacts insulin absorption and effectiveness. Research indicates that healthcare providers often neglect to educate patients on the importance of rotating injection sites [6]. A recent study revealed a concerning number of diabetic patients experiencing inadequate blood sugar control despite regular insulin usage [7].

While the exact cause remains unclear, there is evidence linking this poor glycemic control to insulin administration and associated skin complications. Injecting insulin into areas affected by lipodystrophy can result in unpredictable absorption, potentially leading to unstable blood sugar levels and unexpected hypoglycemia [8, 9].

Achieving optimal glycemic control remains a significant challenge worldwide. A survey found that only around 39.7% of diabetes patients in China met the standard criteria for optimal glycemic management [defined as having a glycated hemoglobin (HbA1c) level below 7%]. In contrast, statistics from the USA have shown approximately 50.1% of diabetic patients to have HbA1c levels below 7% [10]. An increasing number of individuals have been now reported to use insulin therapy to manage their diabetes after finding that their treatment with oral antihyperglycemic drugs has not been effective. Insulin therapy is used by approximately 61.5% of Chinese patients with Type 2 Diabetes (T2D). Asian patients typically choose premixed insulin as their first insulin treatment, in contrast to Western patients. A retrospective review of insulin therapy data has revealed that premixed insulin is provided substantially more frequently (77.3%) in Chinese patients with T2D than basal (11.8%) and prandial (10.9%) insulin [11, 12]. As insulin injection site rotation is anticipated to play a significant role in nursing responsibilities for managing diabetes, this study aimed to assess the extent to which rotating injection sites impact the occurrence of lipohypertrophy and glycemic control in patients with diabetes.

2. MATERIAL AND METHODS

2.1. Research Hypothesis

Diabetic patients who follow insulin injection site rotation have less lipohypertrophy and thus more glycemic control than those who do not follow it.

2.1.1. Study Design

A quasi-experimental research design with a pretest-posttest and a control group was utilized in this study.

2.1.2. Setting

The study was conducted at the medical outpatient clinic of Sohag University Hospital.

2.1.3. Subjects

Patients regularly following up at the diabetes specialist outpatient clinics were recruited to serve as study subjects. Statistical power analysis of patients admitted to Sohag University Hospital's medical outpatient clinic was used to determine the sample size. The sample size was estimated using Epi info 7 with the subsequent parameters: number of patients: 70/three months; level of confidence: 95%; error margin: 5%; rate of prevalence: 50%; and minimum sample size: 60 patients.

We used the G*Power software to perform the power analysis and determined if the sample size was effective or not based on the following equation:

Standard Error (Proportions)

$$SE(\hat{p}) = \sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

Based on a sample size of 70 patients, a 95% confidence level, a margin of error of 5%, and a prevalence rate of 50%, the power analysis has suggested the sample size as adequate to achieve the desired precision. The confidence interval width for the proportion has been found to be within acceptable limits, indicating the study to have sufficient power to detect the prevalence rate with the given parameters.

2.1.4. Inclusion Criteria

Patients with type I or II diabetes mellitus who had been using multiple insulin injections for one year or less were included with an age range between 18 and 80 years. Also, patients were supposed to be using an insulin syringe and taking two daily insulin doses.

2.1.5. Exclusion Criteria

The following individuals were excluded from entering the study: women giving birth to their babies or those intending to get pregnant; individuals having acute metabolic diabetes complications, such as hyperosmolar state or ketoacidosis; individuals with severe side effects, such as end-stage renal disease or cardiovascular disease; those with inadequate adherence and erratic exercise and nutrition, or those with other

eye conditions impeding their vision, such as severe retinopathy or cognitive impairment. In addition, individuals with congenital lipodystrophy and those utilizing insulin pumps were excluded.

2.1.6. Measurements

In order to obtain the required data, two tools were used: I: Bio-sociodemographic and clinical data sheet; age, sex, Body Mass Index (BMI), duration of insulin use, time since DM diagnosis, length of the needle, frequency of needle change, and rotation of insulin injecting site were some of the demographic and clinical data that were obtained from patients' medical records and interviews. Co-morbidities and glycosylated hemoglobin levels (HbA1c) have also been recorded.

The researchers designed this tool after consulting pertinent literature. With the exception of glycosylated hemoglobin (HbA1c), which was measured six months after the initial interview to evaluate glycemic management, all the data in this tool were only obtained once, at the initial patient interview. Based on the American Diabetes Association's (ADA) categorization, it was noted that the controlled HbA1c was less than 7% [13 - 15].

II: Using a lipohypertrophy evaluation sheet, by visually inspecting and palpating the injection sites, the degree of lipohypertrophy was observed. A grade of 0 indicated no changes, a grade of 1 indicated visible hypertrophy of fat tissue but palpably normal, and a grade of 2 indicated massive thickening of fat tissue with firm consistency. The location of LH was also noted by the researchers. The researchers created this tool using pertinent literature as the basis [16, 17].

2.2. Procedure

The following procedures were followed in order to complete the study: authorization was acquired from the Sohag University Faculty of Nursing's Ethical Research Committee. The Sohag University Faculty of Nursing sent an official letter outlining the study's objectives, which was forwarded to the relevant staff at Sohag General Hospital in order to secure consent for data collection. Pilot study: To evaluate the applicability and clarity of the tools and identify potential challenges for the main investigation, a pilot study including six randomly chosen patients who were not included in the main study was carried out. Furthermore, the duration required to respond to the instruments was quantified. The improvements to the tool were made.

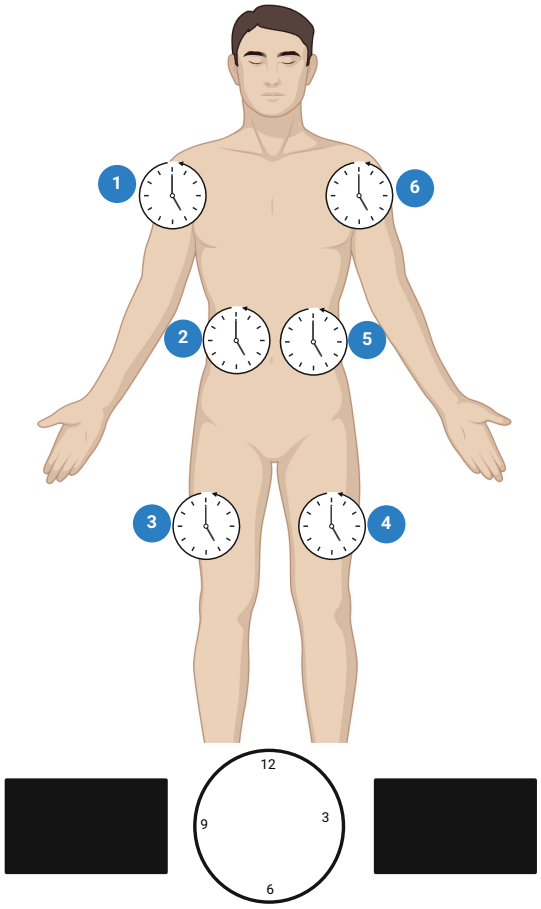

Fig. (1). Anti-clockwise insulin site rotation.

In order to conduct the study, study participants had to be regularly scheduled for follow-up appointments at the diabetes specialist outpatient clinics during the study period. There were sixty patients in total (30 in the trial group and 30 in the control group). To ensure the confidentiality of the data and its use solely for research, the researchers conducted private, one-on-one interviews with every patient in the study and control groups. They were able to get clinical and demographic information, including baseline HbA1c values, from the patients and their records using the interview tool. Additionally, the patient was asked to evaluate and palpate the lipohypertrophy for the first time during the initial interview utilizing tool II.

The researchers did not provide any assistance to the control group during the study period. At the beginning of insulin therapy, the participants' doctors provided them with routine education for thorough training on insulin administration practices in their clinic.

The researchers informed the study group about insulin injection site rotation at the onset of the investigation, in the initial interview, and again at the three-monthly follow-up. The research group was taught the technique of anti-clockwise insulin site rotation through the use of colored pictures. The injection sequence was as follows: the right arm, right side of the umbilicus, right thigh, left thigh, left side of the umbilicus, and finally the left arm (each site was injected in the place of 12, 9, 6, and 3 o'clock, respectively) (Fig. **1**). Multiple colored printed forms of the map helped each patient in the research group remember the locations for insulin injections and the rotation procedure. Every patient in the study and control group had their HbA1c measured three and six months after the initial examination, and they were reviewed six months later for the presence of lipohypertrophy.

2.3. Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 29). Continuous variables have been described using mean Standard Deviation (SD), and categorical data have been described using the percentage. Percentages were compared using the Chi-square test. P values <0.05 were considered statistically significant.

3. RESULTS

Sixty adult diabetic patients with multiple daily insulin injections were divided equally into the study and control groups, representing a mean age of 38.83 and 35.60 years, respectively. Regarding gender, 60% of the study group was female, while 53.3% of the control group included males. The highest percentage of the study group had a university education (40%) and secondary education (36.7%), compared to secondary education (33.3%) and primary education (30%) in the control group. Approximately two-thirds (63.3%, 60%) of patients in both groups were married. There were no statistically significant differences between the study and control groups with respect to the sociodemographic characteristics (Table **1**).

Table **2** represents the clinical data of the study and control groups. The majority of patients in both groups (90%, 80%) had no co-morbidities, while hypertension was comorbid in the other patients in both groups. 30% of patients, both in the study and control groups, had a healthy weight. In the study group, 23% were overweight, 20% were obese class I, and 20% were obese class II. In the control group, 33% of patients were overweight, 16.7% were obese class I, and the same percent were obese class II. Regarding the type of diabetes, 56.7% of the study group and 70% of the control group had type I DM with a duration of a month to less than 6 months receiving insulin within 63.3% of the study group and 53.3% of the control group. Concerning the needle length, 36.7% of the study group and 33.3% of the control group used a 6 mm needle. 26.7% of the study group and 30% of the control group used 8 mm needles. An equal percentage of patients were using 5 mm needles. A minority of patients in the study and control groups, *i.e.*, 10% and 6.7%, used 4 mm needle length. 50% of patients in the study group and 56.7% in the control group changed the needle after 2-3 injections, while 43.3% and 40% of the study and control groups changed the needle after 4 or more injections. There were no statistical significance differences between the study and control groups in relation to the clinical data (Table **2**).

Table 1. Distribution of sociodemographic data among the study and control groups (n=60).

Socio-demographic Characteristics	Groups				Significance
	Study (n=30)		Control (n=30)		
	No.	%	No.	%	
Age (years)					-
Mean (SD)	38.83±14.43		35.60±13.415		t= 0.899 (0.373)
Gender					
Female	18	60.0	14	46.7	
Male	12	40.0%	16	53.3	X^2= 1.071 (0.301)
Level of education					
No schooling	2	6.7	3	10.0	X^2= 2.190 (0.534)
Primary education	5	16.7	9	30.0	
Secondary education	11	36.7	10	33.3	
University or higher	12	40.0	8	26.7	

(Table 1) contd.....

Socio-demographic Characteristics	Groups				Significance
	Study (n=30)		Control (n=30)		
	No.	%	No.	%	
Marital status					
Single	7	23.3	10	33.3	X^2 = 3.890 (0.274)
Married	19	63.3	18	60.0	
Divorced	1	3.3	2	6.7	
Widowed	3	10.0	0	0.0	

Note: - X^2: Chi-square test - t: Student t-test.

Table 2. Distribution of clinical data among the study and control groups (n=60).

Clinical Data	Groups				Significance
	Study (n=30)		Control (n=30)		
	No.	%	No.	%	
**** Co-morbidities**					
Yes	3	10.0	6	20.0	X^2 =1.176 (0 .278)
No	27	90.0	24	80.0	
Body Mass Index (BMI)					
Healthy weight	9	30.0	9	30.0	X^2 =1.045 (0.903)
Overweight	7	23.0	10	33.3	
Obese class 1	6	20.0	5	16.7	
Obese class 2	6	20.0	5	16.7	
Obese class 3	2	6.7	1	3.3	
Mean (SD)	30.30±7.40		29.33±6.29		t= 0.545 (0.588)
Type of diabetes					X^2 = 0.284 (0.749)
Type I	17	56.7	21	70.0	
Type II	13	43.3	9	30.0	
Duration of insulin received in months					
1-<6	19	63.3	16	53.3	X^2 =0.617 (0.432)
6-12	11	36.7	14	46.7	
Mean (SD)	6.05±4.20		5.80±4.27		t= 0.228 (0 .820)
Needle length					
4 mm	3	10.0	2	6.7	X^2 =0.365 (0.947)
5 mm	8	26.7	9	30.0	
6 mm	11	36.7	10	33.3	
8 mm	8	26.7	9	30.0	
Frequency of needle change					
After one injection	2	6.7	1	3.3	X^2 =0.498 (0.779)
2-3 injections	15	50.0	17	56.7	
4 or more injections	13	43.3	12	40.0	

Note: X^2: Chi-Square test- t: Student t-test.

** All participants who had co-morbidities also had hypertension.

Table 3. Effect of insulin injection site rotation on glycemic control (n=60).

Glycemic Control	Study Group (n=30)	Control Group (n=30)	Significance between the Groups	95% CI
-	No. (%)	No. (%)	-	-
HbA1c before the intervention				
< 7%	5 (16.7)	3 (10.0)	X^2 = 0.577 (0.448)	-
> 7%	25 (83.3)	27 (90.0)		-

(Table 3) contd.....

Glycemic Control	Study Group (n=30)	Control Group (n=30)	Significance between the Groups	95% CI
-	No. (%)	No. (%)	-	-
Mean (SD)	8.64± 1.28	8.52± 1.11	t= -0.397 (0.693)	(-0.499 to 0.745)
HbA1c after 3 months of intervention				
< 7%	7 (23.3)	2 (6.7)	X^2 = 3.268 (0.071)	-
> 7%	23 (76.7)	28 (93.3)		-
Mean (SD)	8.14 ±1.30	8.57±1.13	t= -1.369 (0.176)	(-1.066 to 0.201)
HbA1c after 6 months of intervention				
< 7%	12 (40.0)	2 (6.7)	X^2 =9.317(0.002)	-
> 7%	18 (60.0)	28 (93.3)		-
Mean (SD)	7.75± 1.25	8.65±1.14	t= -2.898 (0 .005)	(-1.521 to -0.278)

Note: X^2: Chi-square test, t= independent t-test.

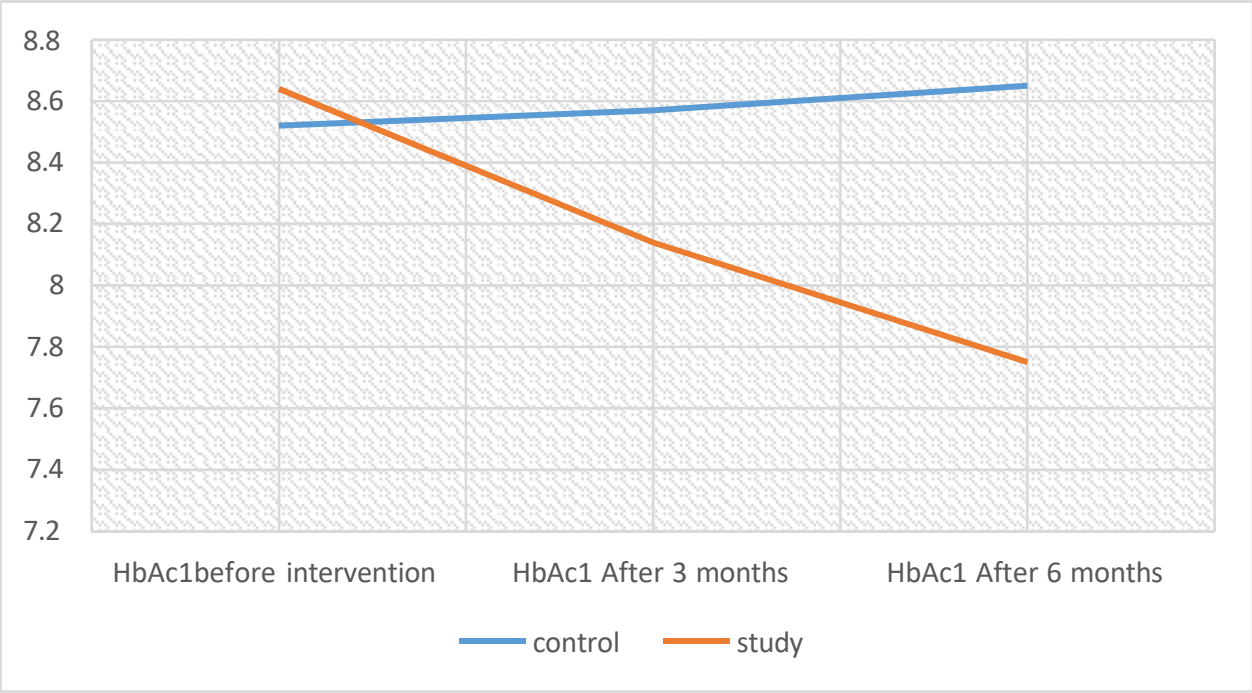

Fig. (2). Glycemic control in patients with diabetes before and after the intervention.

A marked reduction in HbA1c in the study group was noticed as follows: HbA1c level was less than 7 in 40% of patients after 6 months of intervention, 23.3% of patients after 3 months of intervention, compared to 16.7% before any intervention. In the control group, 90%, 93.3%, and 93.3% of patients had more than 7 HbA1c before intervention, and after 3 and 6 months of follow-up without intervention (Table **3** and Fig. **2**).

Table 4. Effect of insulin injection site rotation on lipohypertrophy (n=60).

Lipohypertrophy Assessment	Study Group (n=30)	Control Group (n=30)	Significance between the Groups
-	No. (%)	No. (%)	-
Lipohypertrophy assessment before the intervention			
No change	15 (50.0)	8 (26.7)	X^2 = 3.458 (0.177)
Grade 1	9 (30.0)	13 (43.3)	
Grade 2	6 (20.0)	9 (30.0)	
Lipohypertrophy site	n =15	n = 22	-
Abdomen	3 (20.0)	4 (18.2)	X^2 = 0.048 (0.977)
Thigh	3 (20.0)	5 (22.7)	
Arm	9 (60.0)	13 (59.1)	

(Table 4) contd.....

Lipohypertrophy Assessment	Study Group (n=30)	Control Group (n=30)	Significance between the Groups
-	No. (%)	No. (%)	-
Lipohypertrophy assessment after 6 months of intervention			
No change	21 (70.0)	4 (13.3)	$X^2 = 3.268$ (0.000)
Grade 1	6 (20.0)	11 (36.7)	
Grade 2	3 (10.0)	15 (50.0)	
Lipohypertrophy site	n = 9	n = 26	-
Abdomen	2 (22.2)	6 (23.1)	$X^2 = 0.391$ (0 .823)
Thigh	3 (33.3)	6 (23.1)	
Arm	4 (44.4)	14 (53.8)	

Note: X^2: Chi-Square test.

**All patients who did not perform insulin site rotation or used incorrect insulin site rotation technique were considered as not doing the rotation.

A significant reduction was noticed in the lipohypertrophy grade during the 6-month assessment of the study group. Before the intervention assessment, 50% of the study group and 73% of the control group had lipohypertrophy ranging from grade 1 to grade 2. In the 6-month assessment, 30% of the study group and 80% of the control group had lipohypertrophy ranging from grade 1 to grade 2. Regarding the site of lipohypertrophy, in the initial assessment of the study group, the arm accounted for the highest percentage (60%), followed by 40% for both the abdomen and thigh. These percentages were reduced after 6 months of intervention to 44.4 for the arm site, 22.2% for the abdomen, and 33.3% for the thigh. In the initial assessment of the control group, the arm accounted for the highest percentage (59.1%), followed by the thigh (22.7%) and the abdomen (18.2%). After 6 months of assessment, the percentage did not significantly change, demonstrating 53.8% for the arm site, 23.1% for the abdomen, and 23.1% for the thigh (Table **4**).

4. DISCUSSION

Lipohypertrophy usually refers to adipose cell hypertrophy due to the lipogenic effect of insulin. It presents as soft dermal nodules within the normal surface epidermis. It is the most common dermatological complication of insulin therapy. It also affects the diabetic patients' glycemic control and subsequent doses of insulin. Many factors play a role in the incidence of lipohypertrophy, such as the insulin injection site, technique, and dose [18, 19, 20]. Therefore, this study has investigated the effect of insulin injection site rotation on the incidence of lipohypertrophy and glycemic control in patients with diabetes. To the best of our knowledge, this is the first published study that has drawn a simple map to be followed for patients as a guide for rotating sites of injections.

The study results have revealed the mean age of the participants to be 38.83 and 35.60. The majority of the study group comprised females, while there were more males in the control group. The education level of the participants ranged from university to primary education, and the majority of them were married having no major comorbidities. The only comorbid condition noticed was hypertension. The majority suffered from type I DM with an insulin injection duration from one to less than 6 months. The frequency of injections ranged from two to more than four times daily. It is regrettable that there was still a relatively high prevalence of LH-affected patients as it was found to be 50% in the study group and 73% in the control group at the initial assessment. Moreover, a marked reduction in HbA1c level was noticed among the study group at post-three- and six-month assessments, reflecting a positive impact of the insulin site rotation technique on glycemic control. In addition, a significant reduction was noticed in the lipohypertrophy incidence and grade during the 6-month assessment compared to the pre intervention assessment. In our study, the prevalence of lipohypertrophy in the study and control groups before the intervention was 50% and 43.30%, while at post 6 months' intervention, it was 30% and 86.7%, respectively, representing a marked reduction in incidence for the study group and maximum positive impact and clinical significance of insulin site rotation technique.

Previous studies' [21, 22] results have been found to be in the same line with our study results as they have illustrated the problems, such as lipoatrophy, Lipohypertrophy (LH), allergy, and abscess formation to be among the dermatological complications of insulin injection therapy. A study [20] reported the repeated use of the same region as associated with skin-related complications of insulin therapy, especially LH. Furthermore, the authors of a study [19]confirmed that poor technique and repeated use of insulin administration sites may result in impaired dermatological appearance as well as disruption of glycemic regulation, high hemoglobin A1c (HbA1c) levels, unexpected hypoglycemia (due to the absorption defect in lipohypertrophy), insulin absorption defects, and consequently, a higher insulin requirement, resulting in higher healthcare costs.

On the contrary, Al Jaber *et al*. [23] found the rotating insulin injection site to have no significant relationship with LH development. They attributed this lack of relationship to the fact that patients randomly rotate injection sites. It is worth noting that for many years, studies [24] have reported rotating insulin injection sites to provide better blood glucose control and improve LH. Furthermore, site rotation has also been reported to increase insulin absorption, resulting in an overall reduction of insulin doses by 2-4 units.

The findings of the present study have been found to be in accordance with previous studies [23], explaining that if repeated local insulin injection is carefully avoided, lipohypertrophy is frequently reversible. It can also be avoided by adhering to proper injection techniques with systematic site variation. The most important and modifiable factors for reducing insulin-related lipohypertrophy in patients with type 1

diabetes are the rotation of injections across a vast area and the usage of rapid plus long-acting insulin analogs. Education of both doctors and patients on recognizing and treating lipohypertrophy is advisable.

In order to extend our study results to assess the effect of insulin site rotation on glycemic control, previous results [25] have found a correct insulin injection technique to be essential for optimal glucose control in people with diabetes. Injecting in a zone of lipohypertrophy, insufficient rotation and frequent reuse of insulin needles may all contribute to a suboptimal glycaemic control (HbA1c), an increased risk of hypoglycemic events, and consequently, an increase in diabetes-related costs.

Moreover, a study [26] aimed at assessing the ability of a 6-month intensive, structured patient education program to prevent poor injection habits and related complications and costs in a large group of outpatients with type 2 DM. The results have revealed intensive education to lead to consistently improved metabolic results, a lower insulin requirement, and for the first time, decreased overall healthcare costs in the target population. The authors also recommended that such positive effects should encourage institutions to resolve the intractable problem of LH by providing healthcare teams with economic incentives to carry out intensive, specialized patient education on correct injection techniques. Additionally, LH development has been reported to be associated with several factors and lead to significant fluctuations in blood glucose levels; thus, sufficient attention should be paid to investigating the underlying mechanism of LH [27, 28].

CONCLUSION

The implications of our study are striking; patients do not have to wait for a long time to see improvement in the most important clinical parameters of glycemic control, incidence, and severity of lipohypertrophy. These improvements can be expected early enough in the course of anti-clockwise insulin site rotation to motivate patients. Additional studies are needed to address whether the intervention leads to reduced times and doses of insulin and has a role in minimizing short and long-term diabetic complications.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed the results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
HbA1c	=	Glycolated Hemoglobin

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research has received approval from the ethical research committee of the Faculty of Nursing at Sohag University, Egypt. The approval number assigned to this study is No. (160).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee, and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

A written informed consent was obtained before data collection after an explanation of the study's aim. Autonomy, secrecy, and the protection of data were asserted. Patients' right to withdraw at any time of research participation was considered and respected.

STANDARDS OF REPORTING

TREND guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analysed during this study are included in this published article.

FUNDING

None.

CONFLICT OF INTEREST

The authors have declared no conflict of interest, financial or otherwise.

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Declared none.

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