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Frequency of lipodystrophy induced by recombinant human insulin

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Abstract. – *Backgroud and Objective:* **Lipodystrophy is a potential clinical complication induced by insulin therapy, and it is believed that its frequency has been reduced by using recombinant human insulin. Aim of this study was to determine the frequency of recombinant human insulin induced lipodystrophy in diabetic patients.**

Materials and Methods: **This cross sectional study was done on 220 diabetics referring to Imam Educational Hospital of Sari Township in 2007-2008 who had been under treatment with recombinant human insulin at least three months before.**

First, the anthropologic and clinical features of the patients were recorded in questionnaire, then all of the patients were examined clinically for lipodystrophy. In all patients, glycosylated hemoglobin (HbAIC) was measured for control of the blood glucose. The obtained data were analyzed by the descriptive statistical methods, t-test and 2 test.

Results: **From the total 220 diabetics under study, 35 (15.9%) had insulin induced lipodystrophy, of them 32 (14.5%) had lipohypertrophy and 3 (1.4%) with lipoatrophy. Factors such as age, sex, level of education, body mass index (BMI), type of diabetes, period of using insulin and injection site had significant influence in development of insulin induced lipodystrophy ($p<0.05$).**

Conclusions: **Findings of this study revealed that despite using a recombinant human insulin, the frequency of the lipodystrophy particularly of lipohypertrophy still remained high level. Therefore, a regular examination of the diabetic patients for this complication is necessary, specially in the individuals who have a defective control on their blood glucose level.**

Key Words:

Diabetes, Lipodystrophy, Lipohypertrophy, Lipoatrophy.

Introduction

Diabetes mellitus (DM) includes group of common metabolic disorders, having common characteristics with hyperglycemia phenotype. DM is divided in type 1 and type 2[1]. Development of technology in the last 20 years has changed the life style and the conditions of people, resulted increase in number of diabetic patients and as well as in number of insulin users[2]. Complications of DM involve different organs, particularly of blood vessels, eyes, kidneys, nervous system and skin[3]. Though using of insulin helps in better control of diabetes, but its injection is associated with some problems such as dermal complication which worsens increasing the use of insulin[2]. Lipodystrophy, the common complication of subcutaneous insulin injection, comprises lipoatrophy and lipohypertrophy, it influences insulin absorption and leads to disorder in patient's blood glucose control[4]. Lipoatrophy, defined as a lesion due to subcutaneous lipid tissue atrophy[5], has immunologic bases and is a reaction induced by lipolytic components and impurities of some insulin preparations[4].

Lipohypertrophy, a swelling lesion, soft and benign form of lipid tissue[6-9] is due to insulin lipogenic property[3,10]. When insulin is injected repeatedly in a site, the hypertrophic lipid cells replace mid derm collagen[3]. Pain sensation diminishes in the lipodystrophic areas. Therefore, patient prefers injection at that site, worsening dystrophy at the area[4,11-14].

Though prevalence of insulin lipoatrophy in the past was approximately 15%-55%[15,16]. However, due to providing a pure recombinant human insulin and to the increase of patients' awareness, this complication has been declined[4,17]. Lipohypertrophy is the most common dermal complication, associated with insulin injection[4-8]. Few studies have revealed that its prevalence in the patients treated with recombinant human insulin still remaining high[18,19]. This phenomenon is estimated in 40% type II diabetics and in 20% to 30% type I[6,8,20].

Factors influencing the development of lipohypertrophy have been cited as the amount of time in-

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sulin has been used, gender, BMI, injection site, rotation of sites, the use of pen as opposed to syringe and the frequency needles are changed[6,9,11,12,20].

The lipodystrophy leads to metabolic control disorders in the diabetic patients and consequently an increase of developing complications[4,7].

Considering the use of recombinant human insulin and lack of proper data about the after use of insulin results in the diabetic patients in Iran, this study was designed to determine the frequency of insulin induced lipodystrophy in a cohort of the diabetic patients in 2007-2008.

Materials and Methods

This descriptive cross sectional study was done on 220 diabetic patients under treatment with recombinant human insulin and referring to Diabetes Center of Imam Educational Hospital of Sari Township, Iran. Number of the study cases was estimated 220, considering p=30% (mean of lesion prevalence by studying the relevant literatures from the other societies), α coefficient = 5% and d value (deviation coefficient) = 0.06.

Sampling was done in a sample method and the patients who had been under insulin therapy for at least three months before and referring for treatment were enrolled for the study.

The diabetic women with pregnancy were excluded. After obtaining informed consent from the patients, first the variables of age, gender, level of education, period of suffering diabetes, type of diabetes, duration of insulin treatment, the type and amount of daily injection of insulin, height, weight and BMI were recorded in a questionnaire. For the evaluation of the lipodystrophy in the injection site, all of the subjects were examined by one specialist physician, through observation and palpation technique.

Presence and absence of lipodystrophy and the place of dystrophy were recorded. All of the study subjects were evaluated for blood glucose and HbA1C. HbA1C was measured by HPLC (High Performance Liquid Chromatography) method with **hb gold** kit prepared by Drew Scientific Itd Company, UK.

Statistical Analysis

The obtained data entered SPSS software (Version 10, SPSS Inc, Chicago, IL, USA). The frequency and percentage were calculated. The clinical and anthropologic characteristics of the patients under study were evaluated in percentage and the obtained results were expressed in mean. For comparison of quantitative variables between the lipodystrophy and nonlipodystrophy groups, t-test and ANOVA were used and χ^2 test was used for comparison of qualitative variables.

In determining the role of influencing factors in development of lipodystrophy, multivariate logistic regression analysis was used. p value of less than 0.05 was considered significant.

Results

From total number of 220 diabetics under study, 60 (27.3%) were men, 160 (72.7%) women and age ranged 4 to 78 years with mean of 49±17.9 yrs. Mean duration of suffering diabetes was 14±8.5 yrs (3 months to 41 yrs) and mean duration of insulin therapy was 5.4±6 yrs (three months to 31 yrs). The study subjects, 56 (25.5%) were diabetes type 1 and 164 (74.5%) type 2. Also 37.3% of them injected insulin only one site, whereas 41.4% from two sites and 21.3% from three sites (rotation).

We found insulin induced lipodystrophy in 15.9% of the cases, of them, 14.5 were lipohypertrophy and only 1.4% had lipoatrophy. It was demonstrated that 62.9% of the lipodystrophy patients were diabetic type 1 and 37.1% type 2.

The frequency distribution of lipodystrophy in all of the subjects based on the qualitative variables and the comparison of quantitative variables between lipodystrophy and nonlipodystrophy groups are given in the Tables I and II.

Age

The mean age of the lipodystrophic patients in this study was lower than the mean age of nonlipodystrophic subjects, which is statistically significant (p<0.001).

Gender

Frequency of lipohypertrophy was noticed more in men and three women had lipoatrophy which is statistically significant (p<0.001).

Level of Education

Majority of lipodystrophic patients were illiterate or elementary graduates (45.7%), whereas only 11.4% were university graduates; the difference is statistically significant (p<0.01).

Table I. Frequency distribution of lipodystrophy status in 220 under insulin therapy diabetics referring to Imam Educational Hospitals of Sari Township in 2007-2008 based on the qualitative variables of study.

Variables	Dystrophy present	Dystrophy absent	Total	*p*-value
Number of patients under study	35 (15.9%)	185 (84.1%)	220 (100%)	
Gender				
- male	17 (28.3%)	43 (71.7%)	60 (27.3%)	0.001
- female	18 (11.2%)	142 (88.8%)	160 (72.7%)	
Level of education				
- illiterate or elementary	16 (10.9%)	131 (89.1%)	147 (66.8%)	
- guidance school	8 (42.1%)	11 (57.9%)	19 (8.6%)	0.01
- high school	7 (18.9%)	30 (81.1%)	37 (16.8%)	
- university	4 (23.5%)	13 (76.5%)	17 (7.7%)	
Type of diabetes				
- type 1	22 (39.3%)	34 (60.7%)	56 (25.5%)	0.001
- type 2	13 (7.9%)	151 (92.1%)	164 (74.5%)	
Body mass index (BMI)				
<20 (under weight)	9 (50%)	9 (50.0%)	18 (8.2%)	
20-25 (normal)	11 (16.4%)	56 (83.6%)	67 (30.5%)	0.001
25.1-30 (over weight)	10 (13.0%)	67 (87.0%)	77 (35.0%)	
30.1-40 (obesity)	31 (5.6%)	51 (94.4%)	54 (24.5%)	
<40 (severe obesity)	2 (50.0%)	2 (50.0%)	4 (1.8%)	

Body Mass Index

Lipodystrophy was found in 50% of the patients with BMI lower than 20 (under weight), in 50% with BMI more than 40 (severe obese). A statistically significant relationship was found between BMI and lipodystrophy ($p<0.01$).

Diabetes Type

Rate of lipodystrophic occurrence in diabetes type 1 patients was more than in type 2 (62.9% vs. 37.1%). The obtained *p*-value indicated statistically significant difference ($p<0.001$).

Duration of Suffering Diabetes

The duration of suffering diabetes in the lipodystrophic patients compared to the nonlipodystrophic patients did not reveal any statistically significant difference $p=0.34$.

Duration of Insulin Use

Mean duration of insulin use in the lipodystrophic patients compared to the nonlipodystrophic was higher ($p<0.01$) and the lipodystrophy occurred in 38% of those who had been using insulin for more than 15 years.

Type and Rate of Daily Insulin Injection (NPH and Regular)

In this study the rate of daily insulin use and the type of insulin injected in the lipodystrophic patients compared to the nonlipodystrophic indicated statistically nonsignificant difference, $p=0.33$ and $p=0.51$, respectively.

HbA1c

In the present study, level of HbA1c in the lipodystrophic patients was higher than the nonlipodystrophic, indicating a significant difference ($p<0.05$).

Table II. Comparison of quantitative variables between the recombinant human insulin injection induced lipodystrophy and nonlipodystrophy subjects under study (n = 220)

Variable	Dystrophy present	Dystrophy absent	*p*-value
Age (year)	34.6 ± 21.2	49.3 ± 16.3	0.001
Duration of suffering diabetes (year)	12.7 ± 9.2	14.2 ± 8.4	0.34
Duration of insulin therapy (year)	8.4 ± 6.7	4.9 ± 5.7	0.002
Body max index (BMI)	25 ± 6.7	27.4 ± 5.3	0.02
HbA1c (percentage)	9.5 ± 2.2	8.7 ± 1.9	0.03
Rate of daily regular insulin injection (unit)	10.1 ± 10	12.5 ± 11.3	0.51
Rate of daily insulin injection NPH (unit)	31.2 ± 12.9	33.8 ± 17.2	0.33

The Site and Mode of Injection

Analyses showed the rate of lipodystrophy at the injection sites (arms) more than the other areas (thighs and abdomen) which is statistically significant ($p<0.001$). But nonsignificant difference was observed between lipodystrophic lesions and the mode of insulin injection (only one site, two sites or at every three sites), $p=0.96$.

At end of the study, the multivariate logistic regression analysis was performed to know which of the variables independently leads the diabetics to lipodystrophy. The above mentioned analysis showed that the variables such as gender, diabetes type and duration of insulin use independently influence the other factors in development of insulin induced lipodystrophy. Also based on this test, the effect of lipodystrophy on HbA1c of the patients was independent and significant. The variables of age, BMI, and education level are not independently significant and likely their influence on lipodystrophy is depended to the other factors. The results are given in the Table III.

Discussion

Despite the development of new technology and using of recombinant human insulins, the insulin induced lipodystrophic reactions still remained a potential problem. In the present study, the frequency of the lipohypertrophy in 37.5 of the type 1 diabetics and 6.7% type 2 was observed. Whereas the lipoatrophy occurred in 1.8% of type 1 diabetics and 1.2% of type 2. Frequency of the hypertrophy in the report given by Young et al agree with our data[19]. However, Vardar and Kizilci[2] and Teft[20] reported higher rate of 48.8% and 57%, respectively.

Table III. The influence of independent factors in occurring of recombinant human insulin lipodystrophy based on multivariate logistic regression analysis in the subjects under study.

Variable	The estimated Odd ratio	*p*-value
Age	0.994	0.802
Gender	0.313	0.016
BMI	0.989	0.921
Level of education	0.877	0.622
Diabetes type	0.154	0.040
Duration of insulin use	0.076	0.036
Mode of insulin injection	1.048	0.634
HbA1c	1.222	0.045

There is difference between Vardar and Kizilci's data and our findings since their patients used an insulin needle and 2 years under insulin treatment, while our study subjects used a plastic syringe and after three months have been under insulin treatment. Also, in the Teft's[20] study the cases number was lower (83 patients), and the majority of them were type 1 diabetic and the mean duration of using insulin was 13 years, which was more than our study period.

Frequency of the lipoatrophy in our study, similar to the other investigations, could be attributed to the high purity of the administered recombinant insulin[4,7,17]. The reason of high prevalence of lipohypertrophy in the previous cohorts of patients examined was due to administration of impure animal insulin[15,16]. However, despite using a recombinant human insulin, still lipoatrophy is present, and know the reason of this complication requires further exact researches. We have found that the frequency of lipodystrophy in the type 1 diabetics was much higher than in type 2 as confirmed by the other Authors[6,9].

Using the age as variable we have evaluated them as the effective factor in the development of lipodystrophy and observed the higher prevalence of the lipodystrophy in the lower ages and in the younger individuals[6-14]. It is due to the fact that the prevalence of type 1 diabetes is seen more in lower age. The rate of lipodystrophy was higher in the men diabetics. Furthermore, three lipoatrophy cases were seen only in the diabetic women. Several studies indicated the role of gender as an effective factor in the development of the lipohypertrophy[6,11,12,19,20]. Data given by Eisert[14] indicated prevalence rate more high in women too, due, perhaps, the presence of more subcutaneous adipose tissue in women. Also for this finding further studies are required.

The educational level in the subjects of our study was effective in development of lipodystrophy, the higher education in the patients, lower the incidence of lipodystrophy. In this regard, Vardar's data matched our results[2].

The present study demonstrated that individuals with very low BMI (<20) and very high BMI (<40) are at more risk of developing insulin induced lipodystrophy. Many studies attributed the role of BMI as an effective factor in the development of the lipodystrophy[1,6,9,12,20]. Our data disagree with those data given by Vardar and Kizilci[2]. This difference could be due to the different classification of BMI (natural, overweight and obese) used by Vardar and Kizilci[2] while in our study,

BMI was categorized in 5 classes, where patients under weight and very obese were added.

Our study like the other relevant researches[6] suggests the duration of diabetes as an uneffective factor in the development of the lipodystrophy. We found that the period of insulin therapy is very effective in the development of the lipodystrophy in a way that, the more duration of insulin therapy, more likely the increase of lipodystrophy[2,9,11,12,20]. From the view point of anatomic distribution of lipodystrophic lesion there was a relationship between the injection site and likely of developing insulin induced lipodystrophy[6,9,11,12,20].

Hauner et al[6] evaluated the presence of the lipodystrophy more on the abdomen; conversely, in our study it was noticed more on the arm. The reason of this difference may be that, the majority (49.2%) of our patients preferred the insulin injection on the arm while in the Hauner's study the injection site was on arm only in 21.4% of the cases.

In the present study, no difference was observed between the development of the lipodystrophy and the change of the insulin injection site (only one site, two sites or three sites, rotation), whereas most of the previous investigations attributed the development of the lipodystrophy to the mode of the insulin injection or the change of the injection site[6,9,11,12,20].

Vardar and Kizilci[2] showed that the prevalence of hypertrophy in patients using one site of injection or changing the site of every injection and/or changing the injection site randomly, was higher than in the patients changing the site of injection regularly weekly and the rotation.

Hauner et al[6] noticed that the prevalence of the lipohypertrophy was higher in the patients who never changed the site of the injection or forgot changing the injection site.

In our study, the mode of the insulin injection, particularly the injection rotation was not done properly and the majority of the patients (except the group with one injection site), selected the injection site randomly. This data causes difference between our findings and the above mentioned studies. The quicker the insulin absorption, the less the time spending by adipocytes in the development of insulin lipogenic activity. On other hand, the insulin subcutaneous sedimentation influences the immune system in the development of the lipoatrophy. Murao et al[17] in diabetics with lipoatrophy have found that changing to acute insulin absorption and insulin injection site not only led to the recovery of the lesion, but also prevented the development of any new atrophy at injection site.

Our findings showed the effect of insulin induced lipodystrophy on the control of blood glucose. In fact, these patients had higher HbAlc level. This finding could be attributed to the difference of insulin absorption in the lipodystrophic areas[7,8,11,12,13,17,19,21]. Since the blood glucose control in the diabetes is the main aim of preventing systemic complications, it is mandatory a prevention of this cutaneous complication. Despite using new recombinant human insulins, the prevalence of lipodystrophy is still high. The main factor in preventing the development of lipodystrophy in the diabetic patients under insulin therapy is the education. Therefore, it is necessary to recommend to the patients in changing the injection site periodically, and keeping the their weight in ideal conditions. Also the education to the personal of the centers involved in treating the diabetic patients is required. In conclusion, the higher glucose concentrations found in diabetes mellitus result in more haemoglobin being glycated and this has been validated as a test to indicate the degree of hyperglycemia. HbA1c should be less than 6.5%. For the prevention of the complications of diabetes mellitus, specially in the unstable cases, an intensive insulin therapy attempts to simulate normal insulin secretion, with a combination of short-acting and long-acting insulin. Repeated injection of several types of recombinant insulin into the same subcutaneous site can result in the development of lumps under the skin. The lumps are a combination of fibrous tissue and adipose tissue hypertrophy. The blood supply to these regions is poorer, leading to unpredictable (usually worse) absorption of insulin. Insulin sites should be rotated frequently to avoid this adverse effect.

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