OPEN ACCESS

GAVIN PUBLISHERS

Journal of Diabetes and Treatment

Review Article

Thomas J, et al. J Diabetes Treat 4: 1074.

DOI: 10.29011/2574-7568.001074

Relationship between Lipohypertrophy, Injection Techniques and Education in Adults with Type 2 Diabetes: A Systematic Review

Jenny Thomas, Andrew Meal, Gary G. Adams*

The University of Nottingham, Faculty of Medicine and Health Sciences, Queen's Medical Centre, Nottingham NG7 2HA, UK

***Corresponding author:** Gary G. Adams, The University of Nottingham, Faculty of Medicine and Health Sciences, Queen's Medical Centre, Nottingham NG7 2HA, UK. Email: Gary.Adams@nottingham.ac.uk

Citation: Thomas J, Meal A, Adams GG (2019 Relationship between Lipohypertrophy, Injection Techniques and Education in Adults with Type 2 Diabetes: A Systematic Review. J Diabetes Treat 4: 1074. DOI: 10.29011/2574-7568.001074

Received Date: 18 September, 2019; **Accepted Date:** 11 October, 2019; **Published Date:** 15 October, 2019

Abstract

Introduction: This systematic review examines Lipohypertrophy (LH) in patients presenting with Type 1/2 Diabetes (T1/2DM) in relation to education and injection techniques. LH is a condition, which occurs in diabetes individuals at injection sights. The most common method used is palpation in detecting LH, however preventing LH can be challenging due to a number of risk factors associated with LH.

Method: Seven electronic databases were systematically searched for the most appropriate studies to be included. Articles were identified using Critical Appraisal Skills Programme (CASP) for eligibility. Key words were used to search the database. A PRISMA-based systematic review was used to identify studies.

Results: A total of 49 studies were identified for consideration for this review, to consolidate the studies the abstracts were examined and from these 8 studies were deemed appropriate. Three themes identified from the studies were selected: Theme 1, Risk factors in the development of LH; Theme 2, Patient education influences the development of LH and Theme 3, Do injection techniques cause LH?

Conclusion: There are number of risk factors associated with the cause of LH. Education plays a key role in the prevention of LH although this is not without its limitations. Further selective studies are required in order to establish if there is one stand-alone factor.

Keywords: Type 1/2 diabetes; Adults; Education; Insulin injection techniques; Lipohypertrophy

Introduction

Lipohypertrophy (LH) occurs in subcutaneous tissue because of the lipogenic effect of repetitive exposure to insulin [1]. The fat cells enlarge and proliferate resulting in thickened tissue, forming lumps under the skin. LH is associated with suboptimal glycaemic control with Al Hayek reporting a threefold increase of LH in patients whose control was above the current national target (HbA1c - 7%, 86 mmol/L) compared to those within the target range [2]. Insulin injection into an LH lesion attenuates insulin action with subsequent excess glucose exposure, glycaemic variability and augmented threat of severe hypoglycaemia [3]. Recognised risk factors for the development of LH include high BMI, frequent needle reuse, ineffective insulin injection site(s) rotation, size of rotation area, level of education, and interval of insulin exposure [4]. Patient behaviours are important mediators in the level of LH detected, with patients reusing sites that are less painful or more convenient due to ease of access.

This systematic review examines the relationship between lipohypertrophy, injection techniques and education in adults with type 2 diabetes

Method

Search strategy

A thorough systematic literature search was undertaken in Ovid, Cochrane, Google Scholar, Cinahl, Embase, PubMed and Joanna Briggs Institute. A comprehensive systematic electronic database review was undertaken to establish studies containing information on T1/2DM adults, education on Injection Techniques

(IT) in relation to LH. Once selected articles were retrieved, all titles and abstracts were screened, and eligible articles identified for full text inclusion. Studies and participants were excluded if below 18 years, unwell to participate and/or T2DM patients who could not partake in an educational session. In order to select the studies for this review two valid methodological was used; PRISMA (Figure 1) and the Critical Appraisal Skills Programme (CASP) tool [5,6].

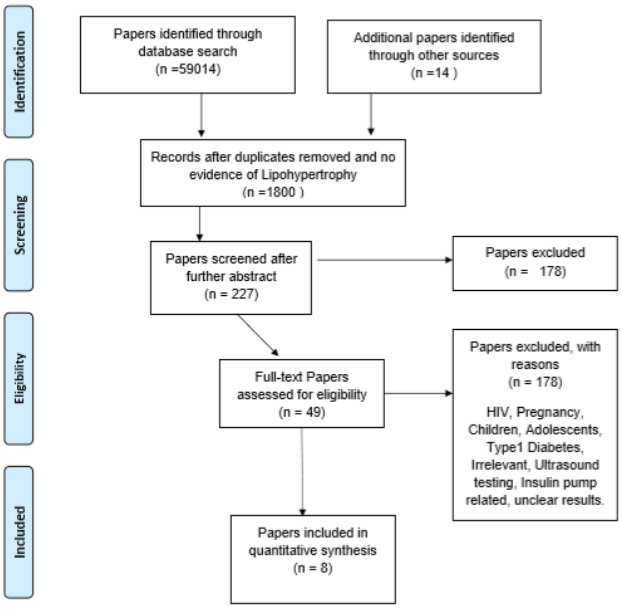

Figure 1: PRISMA Flow Diagram (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Metaanalysis).

Quality Assessment

All 8 studies were identified for inclusion based on their content and study quality of each paper. Both randomised and cohort models within the CASP tool were used.

Ethical Considerations

There was no discrimination regarding the choice of study papers or its contents in relation to religion, gender, ethnicity of its subjects or country.

Results and Discussion

A total number of 49 papers were identified, with 8 studies deemed appropriate based on methodological quality. Three themes were identified : Theme 1, Risk factors in the development of LH, Theme 2, Patient education influences the development of LH and Theme 3, Do injection techniques cause LH?

Theme 1 - Risk factors in the development of Lipohypertrophy (LH)

Three selected studies 3, 5 and 7 [7-9], all considered risk factors to be a key role in the association with the cause of LH.

Lipohypertrophy in these individuals was affected by their level of education, the frequency that they changed needles, the frequency of changing their injection sites and the timeframe over which they had been using insulin. All of the diabetes individuals in Study 3 were given training beforehand about how to rotate an area by using it exclusively for only 1 week. In spite of this, 89 (41.4%) of the group insisted on either using the same area, selecting an area haphazardly or using a different site at every injection. Although study 3 indicated that education, gender, body mass index and the length of needle may not impact the development of lipohypertrophy, the incidence of lipohypertrophy increased as the period of insulin use increased. Moreover, incorrect rotation and failure to change needles are two problems recognised as related to insulin injection techniques.

Study 5 also identified additional factors which influence lipohypertrophy are those who are female, presenting with type 1 diabetes, higher Body Mass Index (BMI) and aberrations in insulin injection rotation. The data suggested that the amount of subcutaneous adipose tissue (female sex and BMI) may be important for the development of lipohypertrophy. Other factors such as age or characteristics of insulin treatment did not contribute to the occurrence of lipohypertrophy. The need to change injection sites regularly was acknowledged by 119 (78.7%) of outpatients, however only 34 (22.7%) followed an organised rotation system. The organised rotation group of patients had the lowest incidence of lipohypertrophy and the least unstable glycaemic profile. The study believed that longstanding incorrect habits promulgate the use of lipohypertrophic areas to inject insulin. Such rooted habits are difficult to change unless the patient is aware of the consequences of injecting insulin into lipohypertrophic areas.

[10] delineated that failing to rotate injection sights is a determinant of LH. They also acknowledged that long-standing habits had occurred and were difficult to change or alter. NICE guidelines suggested that the injection sites should be abdomen, outer thigh, buttocks, and arm [11]. It was reported that accessing some of these areas is difficult especially if the patient is in public or suffers with dexterity such as arthritis [12].

Surucu (Study 7) [7] investigated the frequency of lipohypertrophy and showed that the frequency of lipohypertrophy had decreased in Turkey over a 10-year period. It was considered the decrease stemmed from the patients' preference for shorter needles (4 mm and 5 mm).

Regarding insulin injection technique, lipohypertrophy was shown to be more common in patients who received education on insulin administration from the doctor (65.8%) compared to a nurse. Data showed that the frequency of lipohypertrophy was higher in patients who failed to alternate the injection site (systematic

rotation) 209 (48%) compared to those who did not perform intra-site rotation 159 (63.5%). Needle length, site rotation, changing of needle, injection site used and education were all determining factors affecting the development of lipohypertrophy. Needle length and type of insulin used in individuals with type 2 diabetes revealed that the likelihood of lipohypertrophy was significantly lower in patients using 5 mm needle (31.1%). In addition, the prevalence of lipohypertrophy was significantly higher in patients who failed to systematically alternate the injection site 209 (48.2%). Results discovered that lipohypertrophy was significantly higher in the obese patients. In addition, lipohypertrophy was more common in patients experiencing hypoglycaemia 168 (61.5%).

Young, et al. support this by also identifying that injection of insulin is not without risks including the risk of injecting into the Intramuscular (IM) tissue [13]. This has been previously identified as promoting Pharmacokinetics (PK) and Pharmacodynamics (PD) distortion of the insulin, promulgating poor glycaemic control and possible long-term complications such as renal failure. Understanding the rational for site rotation and the metabolic implications due to the lack of rotation needs to be consistently addressed. In addition, Hauner, et al. also support the findings that those who received education from medical personnel (doctor) are more likely to have LH episodes than those educated by the specialist nurse(s) [14]**.**

Theme 2 -Patient education influences the development of Lipohypertrophy (LH)

Three studies 1, 2 and 8 [15-17] were concerned with the education of the administration of insulin injections and its connection with LH. Clapham, et al. carried out a Cohort study with 75 insulin-injecting patients with the use of an intensive education program [15]. Lipohypertrophy sites decreased significantly by the end of the study, either disappearing completely or shrinking by approximately 50% from its original diameter. Injections into lipohypertrophy decreased by more than 75% by the end. Most patients were not correctly rotating injection sites at the beginning. However, by the end of the followed up period (3-6 months) the rotation of sites had increased 5-fold.

Clapham, et al. [16] also established that, although approximately 33.3% of patients used the 4 mm needle from the outset of the study, by the end of the study, virtually all used the 4 mm needle. With this, the mean HbA1c improved by more than 4mmol/L and there were significantly lower levels of unexpected hypoglycaemia and glucose variability. Total daily doses of insulin dropped by an average of 5.6 IU by study end.

[16] carried out a randomised controlled study on 109 patients in order to establish the impact of injection technique education on insulin-treated patients with clinically observed lipohypertrophy. The intervention group (n = 53) showed a significant decrease in total daily dose of insulin (average at baseline: 54.1 IU) at 3 months and 6 months, attaining > 5 IU after a 6- month timeframe. There were significant decreases in HbA1c (up to 0.5%) at 3 and 6 months in both groups, with no significant differences between the groups. A significant number of patients in the intervention group improved their injection techniques approximately 50% attained this by 3 months contrasted with only a 25% of the control group. By 6 months, 66% of intervention patients achieved either ideal or acceptable injection techniques, while only 33% was realised by the control group. This reduction can not only benefit the patient but also reduce the cost implications [18]. By identifying the importance of treatment for LH including education in Information Technology (IT), isolating the cause of LH is difficult to individualise [19].

In 2016, Li, et al. [17] carried out a hospital Survey in primary, secondary and tertiary settings with a view to visual inspection and palpation for diabetes patients over 1-year duration.

This survey demonstrated 308 (58.01%) incidences of lipohypertrophy in the injection sites of diabetes patients. The lipohypertrophy was associated with the insulin injection duration and the injection interval with 82.33% in the primary care settings 87.08% in secondary care settings. Evidence indicated that patients with lipohypertrophy in primary care settings were the oldest and reluctant to accept guidance/standardisation of insulin injection. The acceptance rate was the lowest consequently. Collectively all 3 studies identified positive results from IT education whether this be from a nurse or GP, despite style of education.

Theme 3 -Do injection techniques cause Lipohypertrophy (LH)?

Berard, et al. 2014 (Study 4) [20] and Frid, et al. 2002 (Study 4) [21] both considered Injection Techniques (IT) and impact on LH.

The study consisted of 503 participants from 55 centres across Canada. Patients and healthcare professionals at each centre completed a separate survey regarding injection technique. 503 individuals (52.9% male, 47.1% female) from 55 centres across Canada participated in the study. Of this group, 25% had type 1 diabetes and 75% had type 2 diabetes. European/Caucasian was the group most highly represented (80.2%); Asian (8.1%), Afro-Caribbean, First Nations and other ethnic groups composed the remaining study population.

Of the individuals studied, 49.9% were taking insulin alone, and 40.3% of subjects used a combination of insulin and oral antihyperglycemic agents to treat their diabetes. The mean length of time on insulin was 7.8 years. The remainder of the study group (9.8%) used combinations of oral antihyperglycemics, insulin and GLP-1 receptor agonists to treat their diabetes. Participants injected insulin with a syringe, pen or insulin pump. Of the study group, only 2.6% injected using a syringe, with 93.8% injecting

using an insulin pen. The remainder of the group used either an alternative device for injection or a combination of devices.

Overall, 402 (80.4%) of participants injected into the abdomen,78 (15.6%) into the thigh, 19 (3.8%) into the arm, 73 (14.6%) into the buttocks and 19 (3.8%) into another area of the body. Study subjects were asked to describe their injection technique by indicating whether or not they used a skin lift ("Pinch-up") and to describe the angle used to insert the needle for injection. Pinch-up method: abdomen = 196 (43.5%); thigh = 98% (51.0%); arm = 66 (48.9%); buttock = 25 (36.8% and another area = 5 (26.3%) (Table1).

Table 1: Characteristics of studies, sample size, and findings.

Study Paper	Author	Country	Type of Study	Study Setting	Study Participants / Sample size	**Characteristics of education intervention.**	**Follow-up strategies**	**Results/Findings/Outcome**
1	**Clapham, et al. (2017)**	United Kingdom (UK)	Prospective Study over (Cohort study)	Clinical settings	75 insulin-injecting patients.	Interventions included the use of an intensive education program and a switch to a 4 mm pen needle.	Followed up for 3–6 months	All injection sites Lipohypertrophy sites decreased significantly by the end of the study, either disappearing completely or shrinking by approximately 50% from its original diameter. Injections into lipohypertrophy decreased by more than 75% by the end. Most patients were not correctly rotating injection sites at the beginning but by the end most were, by a 5-fold margin. Only 1/3 of our subjects used the 4 mm needle at the beginning of the study; however, virtually all did by study end. The mean HbA1c improved by more than 4 mmol/L and there were significantly lower levels of unexpected hypoglycaemia and glucose variability. Total daily doses of insulin dropped by an average of 5.6 IU by study end.

2	**Campions, et al. (2017)**	France	Randomised Controlled Study	Clinic setting	109 patients. 53 in the intervention, 56 controlled. 79(72.5%) men. 58 (53.8%) had Type 1. Age range 18-75 inclusive.	Impact of injection technique education, including use of a 4-mm. pen needle on insulin-treated patients with clinically observed Lipohypertrophy	Follow up in 3 and 6 months	The intervention group (n = 53) showed a significant decrease of total daily dose of insulin (average at baseline: 54.1 IU) at 3 months and 6 months, reaching just over 5 IU after 6 months. No significant decreases between the groups. There were significant decreases in HbA1c (up to 0.5%) at 3 months and 6 months in both groups, with no significant differences between the groups. A significant number of patients in the intervention group improved their injection techniques about half achieved this by 3 months versus only a quarter of the controlled group. By 6 months, two thirds of intervention patients achieved either ideal or acceptable injection techniques, while only 1/3 of controlled group did.
3	**Kizilci, et al. (2006)**	Turkey	Observational and data study	Hospital based setting - Face to face contact	215 Diabetics using insulin for 2yrs + 31 were Type 1 184 were Type 2 women 109 (50.45%) Men 106 (44.9%)	Observation and palpation techniques were used in assessing lipohypertrophy in these diabetic patients.	Had insulin treatment for the last 2 years, all using pen needles	Lipohypertrophy in these individuals was affected by their level of education, the frequency that they changed needles, the frequency of changing their injection sites and the amount of time they had been using insulin. All of the diabetic individuals in this study were given training beforehand about how to rotate an area by using it exclusively for only 1 week. In spite of this, 89 (41.4%) of the group insisted on either using the same area, selecting an area haphazardly or using a different site at every injection. The study showed that education, gender, body mass index and the length of needle did not have an influence on the development of lipohypertrophy. The incidence of lipohypertrophy increases as the period of insulin use increases. In addition, incorrect rotation and failure to change needles are two problems that have been established related to insulin injection techniques.

4	**Berard, et al. (2014)**	Canada	Survey	Diabetes Education Centre	503 participants 267 (52.9%) male 237 (47.1% female. 126 (25%) Type 1 377 (75%) Type 2 European/ Caucasian was most highly represented at 404 (80.2%)	Survey regarding injection technique (i.e. needle length, angle of insertion, incidence of lipohypertrophy, injection routine). Healthcare professionals at the centres also completed a survey regarding their patients' injection techniques	No follow up	Overall, 404 (80.4%) of participants injected into the abdomen,78 (15.6%) into the thigh, 19 (3.8%) into the arm, 73 (14.6%) into the buttocks and 19 (3.8%) into another area of the body. 184 (36.6%) had no explicit injection routine, whereas 158 (31.4%) injected into the same site at the same time each day. Study subjects were asked to describe their injection technique by indicating whether or not they used a skin lift ("pinch-up") and to describe the angle used to insert the needle for injection. Overall, 227 (45.1%) of subjects used pinch-ups for insulin injection, and 458 (91.0%) injected at a 90-degree angle. In subjects who used pinch-ups, 102 (20.2%) released the skin before the end of injection, 210 (41.8%) released the skin directly after injection, 120 (23.8%) released the skin less than 5 seconds after injection and 71 (14.2%) did not know their injection techniques. Most common injection site abdomen by 371 (73.7%). There are 2 discrete areas (e.g. left thigh, right thigh); 470 (93.5%) of subjects used both areas for injecting insulin, and 445 (88.5%) rotated injections within the same site. Lipohypertrophy is one of the major complications, injection routines with patient- and educator-observed lipohypertrophy. Overall, 124 (24.6%) of patients observed lipohypertrophy, whereas only 67 (13.3%) of diabetes educators observed the same complication. Review of the completed surveys 9.74% of diabetes educators did not complete an examination for lipohypertrophy. When participants were asked whether they injected into lipohypertrophic swellings or lumps, 29 (5.7%) indicated that they always injected into these areas, while 87

5	**Gallego, et al. (1997)**	Spain	Clinical and Metabolic-data	Diabetes Unit University Hospital	150 participants 57(38%) male 93 (62%) female 113 (75%) Type 1 37 (24%) Type 2 diabetic patients.	Insulin-treated diabetes of at least one year's duration, type of insulin therapy were evaluated, Injection sites and systematised rotation of injection site were also assessed.	No follow up	Patients who are Female, Type I diabetics, higher body mass index (BMI) and missing rotation of injection sites were all identified as independent risk factors for the presence of lipohypertrophy. The data suggest that the amount of subcutaneous adipose tissue (female sex and BMI) may be important for the development of lipohypertrophy. Other factors such as age or characteristics of insulin treatment did not contribute to the occurrence of lipohypertrophy. The need to change injection sites regularly was acknowledged by 119 (78.7%) of outpatients, however only 34 (22.7%) followed an organised rotation system. The organised rotation group of patients had the lowest frequency of lipohypertrophy and the least unstable glycaemic profile. The study believed that longstanding incorrect habits perpetuate the use of lipohypertrophic areas to inject insulin. Such rooted habits are difficult to change unless the patient is aware of the consequences of injecting insulin into lipohypertrophic areas.
6	**Frid, et al. (2002)**	Europe, 7 countries Sweden, Belgium, Germany, France, Italy, Spain, UK	Clinical Study	22 sites Clinic based	1002 patients 491(49%) male 511(50.9%) female 562 (56%) Type 1 404 (40%) Type 2	Eligible and consenting patients entering the clinic were accessioned. Injections were performed with an insulin pen or syringe or both and participants gave verbal consent to participate.	No follow up	Nearly 702 (70%) of patients inject using a pinch-up injection technique and this practice is associated with improved HbA1c. 301 (30%) of patients in this study reported having lipohypertrophy at any one of their injection sites. 380 (38%) of patients rotated sites each time they injected rapid-acting insulin. Less than 501 (50%) of patients reported having been taught about effective means for preventing lipohypertrophy. Concurrent nurse evaluation found the prevalence to be 27%. Independent risk factors for lipohypertrophy were found to be failure by the patients to check injection sites regularly, failure to rotate sites and longer duration of diabetes.

7	**Surucu, et al. (2017)**	Turkey	Face to face	Clinic - hospital setting	436 Type 2 Diabetic patients 159 (36%)Male 277 (63%) Female	Investigate the frequency of lipohypertrophy and the factors affecting the development of lipohypertrophy.	No follow up	It was determined that the frequency of lipohypertrophy has decreased in Turkey over a 10-years period. It is thought the decrease results from the patients' preference for shorter needles (4 and 5mm). Considering insulin injection technique, lipohypertrophy was found to be more common in patients who received education on insulin administration from the doctor 65.8% as appose to a nurse It was determined that the frequency of lipohypertrophy was higher in patients who failed to alternate the injection site (systematic rotation) 209 (48%) and those who did not perform intra-site rotation 159 (63.5%). Needle length, site rotation, changing of needle, injection site used and education were all determined as important risk factors affecting the development of lipohypertrophy. Needle length and type of insulin used in individuals with type 2 diabetes revealed that the likelihood of lipohypertrophy was significantly lower in patients using 5 mm needle (31.1%). In addition, the prevalence of lipohypertrophy was statistically significantly higher in patients who failed to systematically alternate the injection site 209 (48.2%). Results revealed that lipohypertrophy was significantly higher in the obese category patients. In addition, lipohypertrophy was more common in patients experiencing hypoglycaemia 168 (61.5%).

8	**Li, et al. (2016)**	China	Survey	Hospital Survey in - Primary, Secondary and tertiary settings	736 patients	Visual inspection and palpation were performed for diabetes patients with the disease duration over 1 year.	No follow up	This survey shows the incidences of lipohypertrophy in the injection sites of diabetes patients were 308 (58.01%), and the lipohypertrophy was associated with the insulin injection duration and the injection interval in the tertiary hospitals; 87.08% in the secondary hospitals and the risk factors were the insulin injection duration and the injection area; 82.33% in the primary hospitals and the risk factors were the diabetes duration and the injection interval. Patients with lipohypertrophy in primary hospitals were the oldest and they were reluctant to accept guidance standardisation of insulin injection so that the acceptance rate was the lowest. The survey also noted patients with lipohypertrophy who use the needles repeatedly the insulin needles cost was lower than patients without lipohypertrophy who use the needles once. Education and content was the same in different grade hospitals. Primary and secondary hospitals lack of professional nurse, education cannot be adjusted based on local conditions, using lecture form to save manpower cost and time. Tertiary hospitals set up education clinics, can provide full-time education.

The study also found incorrect injection site along with poor technique, can lead to modified insulin absorption, leading to complications such as hypoglycaemia. Other studies support this by reporting that insulin absorption from LH sites is erratic causing inadequate glucose control [22-23]. The pinch-up technique has also been identified in this study as a good IT, as it enables the patient to inject into the subcutaneous tissue as appose to the intramuscular. Using the pinch-up technique, individuals found their HbA1c was lower, also those leaving the needle in place longer than 10 seconds had an even lower HbA1c reading as appose to those that removed it before 10 seconds.

Berard [20] and Frid [21] are both in agreement. [22] examined 1002 patients 491(49%) male, 511(50.9%) female with 562 (56%) Type 1 and 404 (40%)Type 2 participants. Nearly 702 (70%) of patients injected using a pinch-up injection technique and this practice was associated with improved HbA1c. 301 (30%) of patients reported having lipohypertrophy at any one of their injection sites. 380 (38%) of patients rotated sites each time they injected rapid-acting insulin. Less than 501 (50%) of patients reported having been taught about effective means for preventing lipohypertrophy. Independent risk factors for lipohypertrophy were found to be failure by the patients to check injection sites regularly, failure to rotate sites and longer duration of diabetes.

Conclusion

This systematic review sought to examine the relationship between lipohypertrophy, injection techniques and education in adults with type 2 diabetes. The evidence underlined that education for both staff and patients plays a key role in the identification of LH along with providing vital information on IT and the risk factors associated with immediate risk of LH development. It would appear from these studies that there is not one single main cause of LH but a variety of risk factors associated with the development of LH. It would be justified to suggest that further research into individual risk factors is required.

The evidence has also underlined that education could potentially be the first risk factor of the development of LH, as patients first receive their information regarding insulin injections from a healthcare profession e.g. Doctor or Nurse. Therefore, investigations to establish the health care professionals' training would be an advantage to provide a clearer picture of the information patients receive and understand. More detailed studies would be beneficial based on type, style, participants' age along with who delivers the education and their background knowledge.

In conclusion different countries underestimate the importance of identifying LH and their long-term risk associated to their health suggesting additional more in depth trials are required.

Funding: The authors would like thank the Independent Diabetes Trust

References

1. Richardson, T., Kerr, D. (2003) Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol 4: 661-667.

2. Al Hayek, A.A., Robert, A.A., Braham, R.B., Al Dawish, M.A. (2016) Frequency of lipohypertrophy and associated risk factors in young patients with type 1 diabetes: a cross-sectional study. Diabetes Ther 7: 259-267.

3. Gentile, S., Strollo, F., Corte, T.D., Marino, G., Guarino, G. (2018) Skin complications of insulin injections: a case presentation and a possible explanation of hypoglycaemia. Diabetes Res Clin Pract 138: 284-287.

4. Coninck, C., Frid, A., Gaspar, R., Strauss, K. (2010) Results and analysis of the 2008-2009 insulin injection technique questionnaire survey. Journal of Diabetes 2: pp.168-79. Department of Health (DoH) (2001) National Service Framework for Diabetes: Standards.

5. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. (2009) The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

6. CASP (2018) Critical Appraisal Skills Programme.

7. Vardar, B., Kizilci, S (2007) Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. Diabetes Research in Clinical Practice 77: 231-236.

8. Saez-de Ibarra, L, Gallego, F (1997) Factors related to lipohypertrophy in insulin treated diabetic patients: role of educational intervention. Practical Diabetes international 15: 9-11.

9. Sürücü, H.A., OKur Arslan, H. (2017) Lipohypertrophy in Individuals with Type 2 Diabetes: Prevalence and Risk Factors J Caring Sci 7: 67-74.

10. Ibarra, S., Gallego, F. (1998) Factors related to lipohypertrophy in insulin treated diabetic patients: role of educational intervention. Practical Diabetes International 15.

11. NICE (2016) Type 2 diabetes prevention: population and community-level interventions.

12. Ji, L., Sun, Z., Li, Q., Hirsch, L.J. (2017) Lipohypertrophy—prevalence, risk factors and clinical characteristics of insulin-requiring patients in China. Diabetes Technology Therapeutics 19: 61-67.

13. Young, R.J., Steel, J.M., Frier, B.M. (1981) Insulin injection sites in diabetics - a neglected area? British Medical Journal 283: 349.

14. Hauner, H., Haastert, B., Stockamp, B. (1996) Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. Clinical Endocrinology in Diabetes 104: 106-110.

15. Smith, M., Clapham, L., Strauss, K. (2017) UK lipohypertrophy interventional study. Diabetes research and Clinical Practice 126: 248-253.

16. Campinos C, Floch JPL, Petit C, Penfornis A, Strauss KW (2017) An Effective Intervention for Diabetic Lipohypertrophy: Results of a Randomized, Controlled, Prospective Multicenter Study in France Catherine Campions. Diabetes Technology and Therapeutics 19.

17. Li, F.F., Fu, S.M., Liu, Z.P., Li, Q.F. (2016) Injection sites lipohypertrophy among 736 patients with type 2 diabetes of different-grade hospitals. Journal of Clinical Exp Med 9: 13178-13183.

18. Grassi, G., Scuntero, P., Trepiccioni, R. Strauss, K. (2014) Optimizing insulin injection technique and its effect on blood glucose control. Journal of Clinical and Translational Endocrinology 1: 145-150.

19. Famulla, S., HŐvelmann, U., Fische, A., Coester, H.V., Hermanski, L. (2016) Insulin injection into lipohypertrophic tissue: blunted and more variable insulin absorption and action and impaired postprandial glucose control. Diabetes Care 39: 1486-1492.

20. Berard, L., Cameron, B. (2015) Injection Technique Practices in a Population of Canadians with Diabetes: Canadian Diabetes Association. Canadian Journal of Diabetes 39: 146-151.

21. Strauss, K., De Gols, H., Hannet, I., Partanen, T.M., Frid, A. (2002) A pan-European epidemiologic study of insulin injection technique in patients with diabetes. Practical Diabetes International 19: 71-76.

22. Bermeo-Cabrera, J., Almeda-Valdes, P., Riofrios-Palacios, J., Hindawi, R.M. (2018) Insulin Adherence in Type 2 Diabetes in Mexico: Behaviours and Barriers. Journal of Diabetes Research.