BRAZILIAN JOURNAL OF IMPLANTOLOGY AND HEALTH SCIENCES

ISSN 2674-8169

Lipodystrophy in insulin users: a literature review

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REVIEW ARTICLE

ABSTRACT

Diabetes is a metabolic syndrome of multifactorial origin, resulting from either a lack of insulin or the inability of insulin to regulate blood glucose levels effectively. Since 1921, subcutaneous insulin therapy has been crucial in helping to control glycaemia in diabetic patients. Although it provides benefits, insulin therapy can also lead to complications such as lipodystrophy. This literature review aims to evaluate the characteristics of lipodystrophy in insulin users. Initially, an assessment of the profile of individuals who develop lipohypertrophy due to insulin use was conducted. The authors observed that most patients who reach a critical stage of lipohypertrophy self-administer insulin, which may lead to complacency in adhering to proper administration practices. Some patients reported that discolouration had been present for years, but they felt embarrassed to seek help for the application. In many cases with nodules in the subcutaneous tissue, patients reported that the affected area became painless. The absence of rotation in injection sites is the main cause of the onset of lipohypertrophy. After diagnosis by healthcare professionals and instruction on rotating injection sites, the rate of lipohypertrophy decreased to 8% of patients. Therefore, insulin users require special attention from healthcare professionals to manage lipohypertrophy and other complications associated with insulin therapy.

Keywords: Diabetes. Insulin therapy. Lipohipetrophy.

Lipodistrofia em usuários de insulina: uma revisão da literatura

RESUMO

O diabetes é uma síndrome metabólica de etiologia multifatorial, decorrente da deficiência ou da ineficácia da insulina em regular adequadamente os níveis de glicose no sangue. Desde 1921, a terapia com insulina subcutânea tem sido fundamental para auxiliar no controle da glicemia em pacientes diabéticos. Embora ofereça benefícios, a insulinoterapia pode acarretar algumas complicações, como a lipodistrofia. Esta revisão bibliográfica tem como objetivo avaliar as características da lipodistrofia em usuários de insulina. Inicialmente, foi realizada uma avaliação do perfil das pessoas que desenvolvem lipohipertrofia devido ao uso de insulina. Os autores observam que a maioria dos pacientes que atingem um estágio crítico de lipohipertrofia se autoadministra insulina, o que pode levar a uma acomodação nas práticas corretas de administração da terapia. Alguns pacientes relataram que as manchas já estavam presentes há anos, mas se sentiam constrangidos em procurar ajuda para a aplicação. Em muitos casos com proeminências no tecido subcutâneo, os pacientes relataram que a área afetada se tornava indolor. A falta de rotatividade nos locais de aplicação é a principal causa do surgimento de lipohipertrofia. Após o diagnóstico por profissionais de saúde e instrução sobre a rotatividade dos locais de aplicação, a taxa de lipohipertrofia reduziu para 8% dos pacientes. Portanto, os usuários de insulina requerem atenção especial por parte dos profissionais de saúde para que possam lidar com a lipohipertrofia e outras complicações associadas à insulinoterapia.

Palavras-chave: Diabetes. Insulinoterapia. Lipohipertrofia.

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Dados da publicação: Artigo recebido em 12 de Março e publicado em 02 de Maio de 2024.

DOI: https://doi.org/10.36557/2674-8169.2024v6n5p163-174

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INTRODUCTION

Diabetes is a metabolic syndrome of multifactorial aetiology, characterised by the deficiency or ineffectiveness of insulin in regulating blood glucose levels, resulting in hyperglycaemia. The most common forms of the disease are type 1 and type 2 diabetes mellitus (ADA, 2021).

According to the Brazilian Diabetes Society (SBD, 2019), about 13 million Brazilians suffer from diabetes, and it is estimated that approximately 11% of these individuals use insulin daily. Since 1921, subcutaneous insulin therapy has been fundamental in helping to control blood glucose levels in diabetic patients.

The SBD also highlights that there are two groups of insulin users: those who rely exclusively on this hormone, typically those with type 1 diabetes, and those who use insulin in combination with other medications, characteristic of type 2 diabetes cases. It is noteworthy that the progression of the disease in type 2 diabetes can lead to resistance to oral medications, which often results in the need to introduce insulin use.

Although insulin therapy offers benefits, it is important to note that it can also cause some complications. This study aims to explore this aspect, as a lack of variation in insulin injection sites can lead to the development of lipodystrophy (Gradel et al., 2018).

Lipodystrophy (LDT) is a clinical condition characterised by changes in adipose tissue, manifesting either as lipoatrophy (LA), which is the reduction in the size of adipose cells, or as lipohypertrophy (LH), which is the enlargement of these cells (Brown et al., 2016). According to Dagdelen and colleagues (2018a), LH is the most prevalent form of LDT among diabetic patients, due to the high number of injectable applications.

Cells that develop LH lose the ability to absorb insulin effectively, impairing the achievement of therapeutic goals and causing an imbalance in glucose levels. This may lead the prescriber to increase the insulin dose, believing the issue lies in the lack of efficacy of the insulin, when in fact it is related to the absorption site (Gentile, Strollo & Ceriello, 2016).

The Injection Technique Questionnaire (ITQ) is a clinical tool that allows the assessment of patients' status regarding insulin application. Among the parameters evaluated by the ITQ are the choice of injection sites, the angle of needle insertion relative to subcutaneous tissue, needle length, reuse of needles and syringes, and rotation of injection sites, among other aspects (Calliari et al., 2018).

It is essential for qualified healthcare professionals to be vigilant in detecting lipodystrophy, as many patients who suffer from this condition are unaware of the risk it poses to their treatment (Hussain, Patni & Garg, 2019).

Clinical intervention can significantly contribute to combating this health problem by identifying and correcting the situation through clinical management strategies such as guiding the rotation of insulin injection sites and promoting health education. Through these measures, therapeutic goals can be achieved with appropriate doses of insulin.

METODOLOGY

This qualitative and descriptive literature review aims to evaluate the characteristics of lipodystrophy in insulin users.

Search Strategy: The search was conducted in the PubMed database using the descriptors "lipodystrophy and diabetes" and "lipodystrophy and insulin." The filters applied included publications from 2011 to 2021, human studies, and the English language.

Inclusion and Exclusion Criteria: Articles selected for the review were those that addressed lipodystrophy in insulin users and were available in English, published between 2011 and 2021, focusing on clinical and observational studies. Studies that did not directly address the relationship between lipodystrophy and insulin or were outside the specified time frame were excluded.

Study Selection: The selection of articles was conducted in stages. Initially, titles and abstracts were reviewed to assess their relevance to the topic. Then, the selected articles underwent a full-text review to confirm their suitability for the inclusion criteria.

Quality of Studies: The methodological quality of the included studies was evaluated using a standardized checklist, considering criteria such as study design, sample size, validity, and reliability of results.

Data Extraction: Data were extracted from each selected article, including information on characteristics of lipodystrophy, types of insulin used, management strategies, and the impact on patients' quality of life.

Synthesis of Results: The results were synthesized qualitatively, highlighting the most relevant characteristics of lipodystrophy in insulin users, as well as clinical management strategies.

Limitations: Among the limitations of the review, the limited number of included articles and the exclusive focus on English-language publications stand out. Furthermore, the lack of results from the SciELO and BVS databases may limit the scope of the review.

Additional Data: Data from the Brazilian Diabetes Society were also used to supplement the review and provide context on the prevalence and characteristics of lipodystrophy in insulin users in Brazil.

RESULTS AND DISCUSSION

Profile of Insulin Users with Lipodystrophy

The research began with the analysis of the profile of individuals who develop lipodystrophy as a result of insulin use. The eight reviewed articles included a total of 4,138 individuals from various regions around the world. Table 1 illustrates the data collected on this studied population.

Table 1. Profile of Insulin Users with Lipodystrophy

Characteristics	Percentage (%) / 4,138 patients
Sex	Male (63%), Female (37%)
Age	0-21 years (15%); 21-55 years (7%); Over 55 years (78%)
Duration of insulin use	Less than 5 years (8%); 5-8 years (34%); Over 9 years (58%)
Number of daily injections	1-2 injections (12%); Over 2 injections (88%)
Daily dosage	20-40 units (49%); Over 40 units (51%)

Type of insulin used	Regular (37%); NPH (46%); Lispro and aspart (8%); Glargine (9%)
Needle thickness	4mm (45%); 5mm (34%); 6mm (21%)

Source: Prepared by the authors (2021)

The prevalence of lipodystrophy among men who use insulin has been associated with two significant factors. Kalra and colleagues (2017a) highlight that the first factor is the presence of more pronounced adipose septa in male subcutaneous tissue compared to women. The second factor is the low rotation of insulin injection sites.

Regarding age, individuals over 55 years old were found to lead the prevalence ranking, suggesting that there is a need for greater awareness in this age group about the correct techniques for insulin application. According to Dagdelen and others (2018a), a significant number of children and young people are also affected by lipohypertrophy (LH), typically associated with the frequency of daily injections and the duration of insulin use.

In terms of daily dosage, no significant disparities were observed in the units of insulin applied. However, there are considerable differences in the types of insulin used. Baruah and co-authors (2017) contribute to the subject by stating that many patients do not usually reconstitute insulins such as NPH, which is a crystalline insulin.

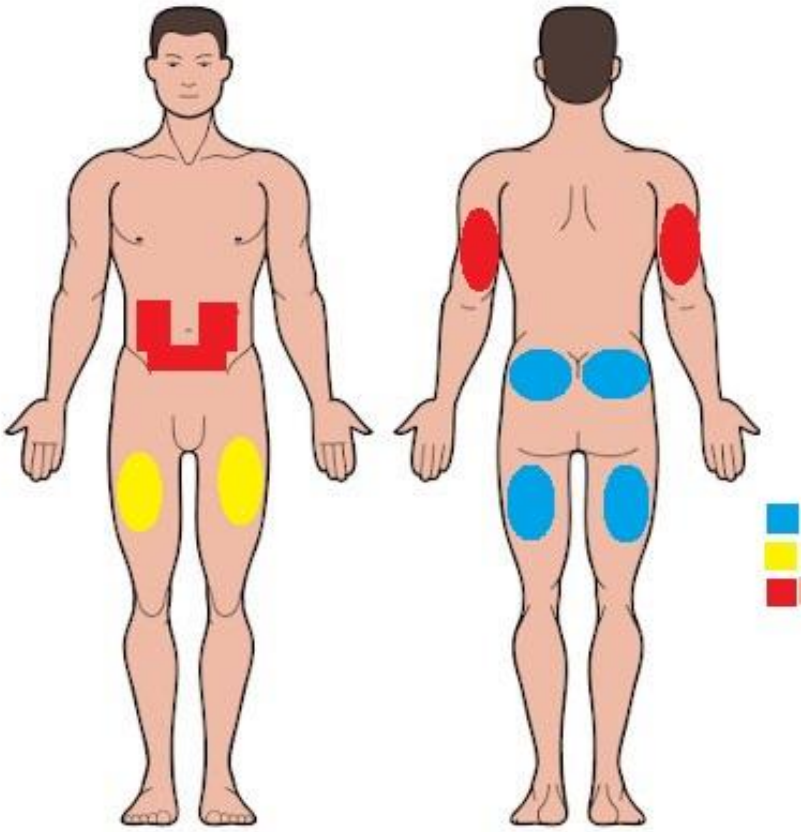
When applying the Injection Technique Questionnaire (ITQ), Kalra and colleagues (2017b) identified a direct relationship between needle thickness, duration of insulin use, and the number of daily injections. It was observed that, as the years pass or with an increase in daily use, there is a tendency to reduce needle thickness.

Another notable aspect of the profile of these individuals is the practice of self-injection. The authors note that most individuals who reach a critical level of lipohypertrophy (LH) administer insulin on their own, which may lead to a relaxation in the correct administration practices. This accommodation can contribute to the worsening of the condition.

Insulin Injection Sites and Severity

This research highlighted the importance of subcutaneous insulin injection sites. Figure 1 illustrates the main sites and the severity with which they are affected.

Figure 1: Insulin Injection Sites and Criticality



Blue Square: Non-Critical, Yellow Square: Critical, Red Square: Very Critical

Source: Prepared by the authors (2021)

Kalra and colleagues (2017b) observed that insulin injection sites, such as the abdomen and the triceps region, exhibited visible protrusions and discolouration. In some cases, palpation revealed hardened areas in the vastus lateralis of the thigh, unlike the lower dorsal regions, which did not display any discolouration.

According to Gentile, Strollo, and Ceriello (2016), levels of tumour necrosis factor (anti-TNF) were elevated in patients with critical conditions of lipohypertrophy (LH). The authors also suggest that there may be a close relationship between an individual's genetics and the likelihood of developing LH.

A notable characteristic in each study was the demonstration of the effects of insulin application on different body parts. Some reports indicated that discolouration had appeared years earlier, but patients felt embarrassed to seek the help of someone

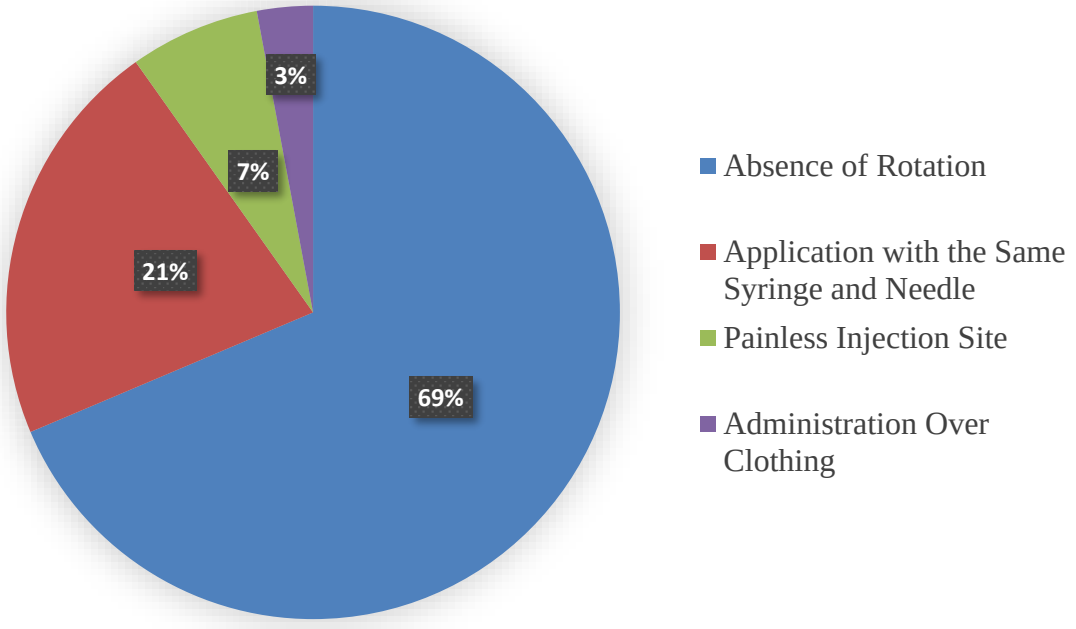
else for administration. Patients with lumps in the subcutaneous tissue reported that the affected area became painless.

These observations highlight the need for more rigorous monitoring of patients, especially those who self-inject insulin, due to the importance of rotating injection sites. It was noted that the back is rarely used, while the abdomen and triceps are overused, which may contribute to problems related to LH.

Causes of LH Development

Figure 2 outlines the causes of LH development.

Figure 2: Lipohypertrophy in Insulin-Dependent Patients



Source: Prepared by the authors (2021)

The absence of rotation in insulin injection sites is the primary cause of lipohypertrophy (LH). Dagdelen and others (2018b) highlight that the lack of alternation in injection sites proved to be a serious issue, with some patients reporting that insulin would spurt out because it could not remain in the subcutaneous tissue due to the hardening of the area.

Regarding the reuse of syringes and needles, many authors reported that although patients were aware of the need to replace these materials, they did not do so due to the associated high monthly cost, as noted by Kalra and colleagues (2017b). Additionally,

the practice of injecting insulin over clothing was observed in some cases among men, although there was no clear rationale for this practice.

Reports of painless sites indicate comfort in insulin administration. Baruah and co-authors (2017) suggest that repeated lesions in the same tissue may lead to the natural release of endorphins, which act as a local anaesthetic. In the case of LH, the additional growth of adipose tissue may inhibit sensory stimuli from neurons.

After healthcare professionals diagnosed LH and provided guidance on rotating injection sites, the rate of LH fell to 8% of patients. Furthermore, glycated haemoglobin, which had previously been around 10.5, dropped to 8.4. Daily insulin doses that exceeded 40 units were reduced to 20 units. These results demonstrate that a simple intervention in this group led to significant improvement in the quality of life of treated individuals.

FINAL CONSIDERATIONS

Therefore, insulin users require special attention from healthcare professionals to manage lipohypertrophy, a significant health issue. Health education is essential to reduce this condition, encouraging rotation of injection sites and advising patients not to overlook potential deformities in medication administration sites.

Moreover, increasing the dose will not correct this disorder, as it is an issue of absorption. The importance of advancing towards less aggressive and more effective methods of administration, such as inhaled insulins, should be emphasised to resolve the patient's clinical condition.

Finally, there needs to be a greater focus on discussions surrounding this topic, as it is of great importance, and research in this area remains limited. It is essential to continue investing in studies and developments to improve the treatment of diabetes patients facing lipohypertrophy.

REFERENCE

AMERICAN DIABETES ASSOCIATION (ADA). Standards of medical care in diabetes – 2020. Diabetes Care.

BARUAH, Manashp; KALRA, Sanjay; BOSE, Saptarshi; DEKA, Jumi. An audit of insulin usage and insulin injection practices in a large Indian cohort. Indian Journal Of Endocrinology And Metabolism, [S.L.], v. 21, n. 3, p. 443, 2017. Medknow. http://dx.doi.org/10.4103/ijem.ijem_548_16.

BROWN, Rebecca J.; ARAUJO-VILAR, David; CHEUNG, Pik To; DUNGER, David; GARG, Abhimanyu; JACK, Michelle; MUNGAI, Lucy; ORAL, Elif A.; PATNI, Nivedita; ROTHER, Kristina I.. The Diagnosis and Management of Lipodystrophy Syndromes: a multi-society practice guideline. The Journal Of Clinical Endocrinology & Metabolism, [S.L.], v. 101, n. 12, p. 4500-4511, dez. 2016. The Endocrine Society. http://dx.doi.org/10.1210/jc.2016-2466.

CALLIARI, Luis Eduardo; CUDIZIO, Laura; TSCHIEDEL, Balduino; PEDROSA, Hermelinda C.; REA, Rosangela; PIMAZONI-NETTO, Augusto; HIRSCH, Laurence; STRAUSS, Kenneth. Insulin Injection Technique Questionnaire: results of an international study comparing brazil, latin america and world data. Diabetology & Metabolic Syndrome, [S.L.], v. 10, n. 1, p. 01-100, 27 nov. 2018. Springer Science and Business Media LLC. http://dx.doi.org/10.1186/s13098-018-0389-3.

DAGDELEN, Selcuk; DEYNELI, Oguzhan; OLGUN, Nermin; SIVA, Zeynep Osar; SARGIN, Mehmet; HATUN, Sükrü; KULAKSIZOGLU, Mustafa; KAYA, Ahmet; GÜRLEK, Cansu Aslan. Turkish Insulin Injection Technique Study: population characteristics of turkish patients with diabetes who inject insulin and details of their injection practices as assessed by survey questionnaire. Diabetes Therapy, [S.L.], v. 9, n. 4, p. 1629-1645, 30 jun. 2018. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s13300-018-0464-7.

DAGDELEN, Selcuk; DEYNELI, Oguzhan; OLGUN, Nermin; SIVA, Zeynep Osar; SARGIN, Mehmet; HATUN, Sükrü; KULAKSIZOGLU, Mustafa; KAYA, Ahmet; GÜRLEK, Cansu Aslan. Turkish Insulin Injection Techniques Study: complications of injecting insulin among turkish patients with diabetes, education they received, and the role of health care professional as assessed by survey questionnaire. Diabetes Therapy, [S.L.], v. 9, n. 4, p. 1615-1628, 30 jun. 2018. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s13300-018-0463-8.

GENTILE, Sandro; STROLLO, Felice; CERIELLO, Antonio. Lipodystrophy in Insulin-Treated Subjects and Other Injection-Site Skin Reactions: are we sure everything is clear?. Diabetes Therapy, [S.L.], v. 7, n. 3, p. 401-409, 25 jul. 2016. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s13300-016-0187-6.

GRADEL, A. K. J.; PORSGAARD, T.; LYKKESFELDT, J.; SEESTED, T.; GRAM-NIELSEN, S.; KRISTENSEN, N. R.; REFSGAARD, H. H. F.. Factors Affecting the Absorption of Subcutaneously Administered Insulin: effect on variability. Journal Of Diabetes Research, [S.L.], v. 2018, p. 1-17, 4 jul. 2018. Hindawi Limited. http://dx.doi.org/10.1155/2018/1205121.

HUSSAIN, Iram; PATNI, Nivedita; GARG, Abhimanyu. Lipodystrophies, dyslipidaemias and atherosclerotic cardiovascular disease. Pathology, [S.L.], v. 51, n. 2, p. 202-212, fev. 2019. Elsevier BV. http://dx.doi.org/10.1016/j.pathol.2018.11.004.

KALRA, Sanjay; MITHAL, Ambrish; SAHAY, Rakesh; JOHN, Mathew; UNNIKRISHNAN, A. G.; SABOO, Banshi; GHOSH, Sujoy; SANYAL, Debmalya; HIRSCH, Laurence J.; GUPTA, Vandita. Indian Injection Technique Study: injecting complications, education, and the health care professional. Diabetes Therapy, [S.L.], v. 8, n. 3, p. 659-672, 13 mar. 2017. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s13300-017-0244-9.

KALRA, Sanjay; MITHAL, Ambrish; SAHAY, Rakesh; JOHN, Mathew; UNNIKRISHNAN, A. G.; SABOO, Banshi; GHOSH, Sujoy; SANYAL, Debmalya; HIRSCH, Laurence J.; GUPTA, Vandita. Indian Injection Technique Study: population characteristics and injection practices. Diabetes Therapy, [S.L.], v. 8, n. 3, p. 637-657, 13 mar. 2017. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s13300-017-0243-x.

SOCIEDADE BRASILEIRA DE DIABETES (SBD). Diretrizes da Sociedade Brasileira de Diabetes (2019-2020). São Paulo: AC Farmacêutica, 2019.