Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Comparative Clinical Effectiveness and Safety of Long-Term Subcutaneous Insulin Injections by Site

Date: September 5, 2007

Research question:

1. What are the adverse events for adult patients receiving long-term subcutaneous insulin injections in the upper arm?
2. What is the comparative clinical effectiveness (absorption rate) of subcutaneously injecting insulin into arms, legs or abdomens of adult patients?

Additional Interest:

3. Guidelines for documenting the rotation of insulin injection sites for staff in long-term care facilities who administer insulin subcutaneously to their patients.

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, CINAHL, The Cochrane Library (Issue 3, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. Abstracts and Internet links are provided, where available.

Results:

1. What are the adverse events for adult patients receiving long-term subcutaneous insulin injections in the upper arm?

Health technology assessments

None were identified

Systematic reviews
None were identified

General guidelines and recommendations
Some information in guidelines listed below

Clinical Studies

Randomized Controlled Trials
None were identified

Observational Studies

1. Shimizu I, Furuya K, Osawa H, Fujii Y, Makino H. A Case of Insulin-induced Localized Lobular Panniculitis with Evidence for the Phagocytosis of Insulin by Histiocytes. *Endocr J* 2007;54(3):477-80. PM:17457015

   Insulin-induced localized lipoatrophy is a well-known localized side effect. Although an immune process has been suggested as its etiology, no definitive evidence has been reported to show that insulin is involved. Here, we report the first evidence for the phagocytosis of insulin by histiocytes as a very early stage of lipoatrophy, which was reproducible in two different lobular panniculitis tissues from a 71 year-old male patient. He had taken a subcutaneous insulin injection in his arms because of a sight disturbance. Since these subcutaneous tumors were likely due to inflammation by insulin, a biopsy sample was taken from the subcutaneous tumor of his right arm with his consent. The primary antibodies for insulin (1 : 200) and CD68 (1 : 50) were obtained from DAKO (guinea pig anti-insulin and mouse anti-human CD68). HE staining revealed the infiltration of mononuclear cells and histiocytes into the subcutaneous fat tissue, and some parts of this tissue had fibrosis with rich collagen fibers. These findings are consistent with a lobular panniculitis. Some histiocytes contained intracellular substances with a positive immunoreactivity to insulin. This activity was reduced when the anti-insulin antibody was preincubated with an excess amount of insulin antigen. The same substances were also positive to CD68. Thus, the phagocytosis of insulin by histiocytes appears to occur in this region. Therefore, the activation of subcutaneous macrophages by the complex of insulin and insulin antibodies may account for the initial autoimmune process

2. Vardar B, Kizilci S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. *Diabetes Res Clin Pract* 2007;77(2):231-6. PM:17303282

   This study examines the incidence of lipohypertrophy in diabetic individuals as well as the factors that have an influence on causing this condition. In consideration of the period of development of lipohypertrophy, the research sampling consisted of 215 diabetics who had been using insulin for at least 2 years. Observation and palpation techniques were used in assessing lipohypertrophy in these diabetics. Data were evaluated using percentages, chi(2) and logistic regression analysis. Results of the study established lipohypertrophy in 48.8% of the individuals comprising the sampling. It was seen that the incidence of 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, the difference proving to be statistically significant ($p<0.05$). In the logistic regression analysis, it was found that the amount of time insulin had been used ($p=0.001$), the frequency of changing injection sites ($p=0.004$) and the frequency of changing needles ($p=0.004$) had an influence on the

development of lipohypertrophy. These results show that the amount of time insulin is used and the procedure for injection both affect the development of lipohypertrophy

3. Swift B. Examination of insulin injection sites: an unexpected finding of localized amyloidosis. *Diabet Med* 2002;19(10):881-2. PM:12358880

2. What is the comparative clinical effectiveness (absorption rate) of subcutaneously injecting Insulin into arms, legs or abdomens of adult patients?

Health technology assessments
None were identified

Systematic reviews
None were identified

General guidelines and recommendations

1. National Collaborating Centre for Chronic Conditions. *Type 1 diabetes in adults. National clinical guideline for diagnosis and management in primary and secondary care*. London (UK): Royal College of Physicians; 2004. Summary available from: http://www.guideline.gov/summary/pdf.aspx?doc_id=6249&stat=1&string=insulin+AND+injection

2. Rotating your insulin sites. In: *BD Diabetes Education*. Franklin Lakes (NJ): BD; 2007. Available: http://www.bddiabetes.com/us/main.aspx?cat=1&id=282

3. Babar I, Gilbert L. *Guidelines for the management of the initiation of insulin in adults.* Worchestershire Acute Hospitals NHS Trust; 2003. Available: http://www.worcestershirehealth.nhs.uk/Intranet1_Library/foi_internet/foi_files/class_9/Clinical_Policies/121004GuidelinesForTheInitiationOfInsulin.pdf.

4. Gallichan M, O'Brien S. *Starting insulin treatment in adults with type 2 diabetes: RCN guidance for nurses*. London: Royal College of Nursing; 2007. Available: http://www.rcn.org.uk/publications/pdf/Starting%20insulin%20in%20adults%20with%20type%202%20diabetes.pdf.

5. King L. Subcutaneous insulin injection technique. *Nurs Stand* 2003;17(34):45-52. Available: http://www.nursing-standard.co.uk/archives/ns/vol17-34/pdfs/v17n34p4552.pdf.

6. International Society for Pediatric and Adolescent Diabetes. Insulin - problems with injections. In: *Consensus guidelines for the management of type 1 diabetes mellitus in children and adoelscents*. The Netherlands: Medical Forum International; 2000. Available: http://www.diabetesguidelines.com/health/dwk/pro/guidelines/ISPAD/09_06.asp.

7. How often do you rotate the insulin injection site? In: *Primary Care Question Answering Service*. London: National Library for Health; 2006. Available: http://www.clinicalanswers.nhs.uk/index.cfm?question=3748.

8. From which of the normal sub-cutaneous injection sites (upper arm, thigh, and abdomen) is insulin absorbed most, and least rapidly? In: *Primary Care Question Answering Service*. London: National Library for Health; 2007. Available: http://www.clinicalanswers.nhs.uk/index.cfm?question=5452.

9. Steel JM. *Diabetes: Injecting insulin - sites and swelling*. Washington DC: Diabetes Research and Wellness Foundation; 2002. Available: http://www.diabeteswellness.net/pdfs/INJECT.pdf#search=%22insulin%20sites%22.

10. Arni R, Bihr MA, Cole M, Cook D, Davis M, et al. Medication: Insulin and Insulin Therapy. In: *Diabetes management in the school setting*. Jefferson City (MO): Missouri Department of Health & Senior Services; 2004. Available: http://www.dhss.mo.gov/diabetes/DMMedications.pdf.

11. European IDDM Policy Group. Targets, insulin, hypoglycaemia, diet and lipids. In: *Consensus guidelines for the management of insulin-dependent (Type 1) diabetes*. Brussels: International Diabetes Federation, World Health Organization; 1993. Available: http://www.staff.ncl.ac.uk/philip.home/iddmch3.htm.

12. Workman B. Safe injection techniques. *Nurs Stand* 1999;13(39):47-53. Available: http://www.nursing-standard.co.uk/archives/ns/vol13-39/v13w39p4753.pdf.

Clinical Studies

Randomized Controlled Trials

None were identified

Observational Studies

1. Johansson UB, Amsberg S, Hannerz L, Wredling R, Adamson U, Arnqvist HJ, et al. Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care* 2005;28(8):2025-7. PM:16043749

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Appendix – Further information:

3. Guidelines for documenting the rotation of insulin injection sites for staff in long-term care facilities who administer insulin subcutaneously to their patients.

The guidelines identified discussed appropriate injection sites, associated absorption rates and addressed the need for rotating sites, yet none provided a template for documenting.

Review articles

1. Hambridge K. The management of lipohypertrophy in diabetes care. *Br J Nurs* 2007;16(9):520-4. PM:17551441

   Lipohypertrophy has been a recognized complication of insulin therapy for many years, yet research shows that its prevalence in insulin-injecting patients with diabetes remains high. The problem for the patient is that the injection of insulin into a site of lipohypertrophy, although painless, may lead to erratic absorption of the insulin, with the potential for poor glycaemic control and unpredictable hypoglycaemia. Despite the important implications of this for diabetes control in insulin-injecting patients, there is a dearth of information and completed research into the condition. This article raises awareness of lipohypertrophy by reviewing the available literature on the prevention, identification and management of the condition from a nursing perspective. Recommendations for medical and nursing practice in diabetes care to improve prevention and management of lipohypertrophy are made

2. Annersten M, Willman A. Performing subcutaneous injections: a literature review. *Worldviews Evid Based Nurs* 2005;2(3):122-30. PM:17040533

   BACKGROUND: Persons using daily subcutaneous injections to administer medicine perform them in different ways and thereby increase the risk of skin complications related to the injection. It is often part of nurses' role to administer medicine and educate the patient in injection technique. Course literature in nursing education, commercial patient education pamphlets, and instructional leaflets do not give consistent advice regarding subcutaneous injection technique. AIM: The aim of this review was to identify the scientific foundation for the technical performance of subcutaneous injections. The question to be answered was: How should a subcutaneous injection be administered to achieve the right dose in the right place with minimum complications? METHOD: The review included a search in three databases, a screening process at abstract level, followed by a quality assessment of included articles. The quality assessment was done independently by two people and followed specific protocols. RESULT: A total of 38 articles were assessed for quality and covered information on dose, location, and complications of subcutaneous injection. The assessed studies are heterogeneous in design and describe different aspects of the subcutaneous injection technique. Therefore, the scientific foundation for technical performance is weak. However, several studies indicate that the amount of subcutaneous fat and appropriate needle length are of high importance for the drug to reach the target tissue. CONCLUSION: More research regarding effective subcutaneous injection technique needs to be done

3. King L. Subcutaneous insulin injection technique. *Nurs Stand* 2003;17(34):45-52. PM:12764975

Insulin injection technique has far greater bearing on glycaemic control than is often recognised. This article discusses the optimal needle length for different injection sites and highlights other crucial aspects, such as needle re-use, importance of adequate mixing of cloudy insulin, and the way pen devices should be stored

4. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol* 2003;4(10):661-7. PM:14507228

The incidence and prevalence of all types of diabetes mellitus is increasing at an alarming rate. Modern therapy involves greater and earlier use of intensive insulin regimens in order to achieve better control of blood glucose levels and reduce the long-term risks associated with the condition. Insulin therapy is associated with important cutaneous adverse effects, which can affect insulin absorption kinetics causing glycemic excursions above and below target levels for blood glucose. Common complications of subcutaneous insulin injection include lipoatrophy and lipohypertrophy. The development of lipoatrophy may have an immunological basis, predisposed by lipolytic components of certain insulins. Repeated use of the same injection site increases the risk of lipoatrophy--with time, patients learn that these areas are relatively pain free and continue to use them. However, the absorption of insulin from lipoatrophic areas is erratic leading to frequent difficulties in achieving ideal blood glucose control. With the increasing use of modified, rapidly absorbed analog insulins (e.g. insulin lispro, insulin aspart) the incidence of lipoatrophy occurring has decreased over recent years. The likelihood of lipoatrophy can be reduced by regular rotation of injection sites but once developed, practical benefits may be obtained by insulin injection into the edge of the area, co-administration of dexamethasone with insulin, or changing the mode of insulin delivery. Lipohypertrophy is the most common cutaneous complication of insulin therapy. Newer insulins have also reduced its prevalence considerably, although its adverse effect on diabetic control is similar to lipoatrophy through impaired absorption of insulin into the systemic circulation. Experience with liposuction at these sites is limited, although good cosmetic results have been achieved. Local allergic reactions to insulin are usually erythema, pruritus, and induration. These allergic reactions are usually short-lived, and resolve spontaneously within a few weeks. Useful adjuncts to managing allergic reactions include addition of dexamethasone to the insulin injection, desensitization to insulin, or a change in delivery system utilizing insulin pump therapy or potentially inhaled insulins when these become available. The use of insulin pump therapy in managing cutaneous complications of insulin therapy is increasing, but this method itself carries risks of abscess formation and scarring. Fortunately, with improved education of patients these are relatively uncommon. Although many of the cutaneous manifestations are decreasing with the use of newer insulins, they may still influence glycemic control and increase the risk of hypoglycemia as well as have a cosmetic impact on a patient. The introduction of novel therapies and newer delivery systems is likely to reduce the cutaneous problems associated with long-term insulin use

Additional references:

1. Fujikura J, Fujimoto M, Yasue S, Noguchi M, Masuzaki H, Hosoda K, et al. Insulin-induced lipohypertrophy: report of a case with histopathology. *Endocr J* 2005;52(5):623-8. PM:16284443

   An 82-year-old woman with type 2 diabetes had been treated with recombinant human insulin for 16 years. She developed large swellings in both sides of her lower abdomen. The masses were soft, painless, and located around her insulin injection sites. Based on the history and clinical features, a diagnosis of insulin-induced lipohypertrophy was made. Total resection revealed that the lesions were composed entirely of fatty tissue. Microscopic examination showed nests of mature adipocytes expanding toward the dermal reticular layer. The hypertrophic adipocytes were twice as large as those from normal subcutaneous areas and contained numerous small lipid droplets. Electron microscopic analysis also revealed a minor population of small adipocytes, suggesting active differentiation or proliferation. Thus, the possible in vivo effects of insulin on adipocytes were clearly observed in this case of insulin-induced lipohypertrophy. To our knowledge, this is the first report of insulin-induced lipohypertrophy with detailed histological examinations

2. Wallymahmed ME, Littler P, Clegg C, Haqqani MT, Macfarlane IA. Nodules of fibrocollagenous scar tissue induced by subcutaneous insulin injections: a cause of poor diabetic control. *Postgrad Med J* 2004;80(950):732-3. PM:15579616

   A 46 year old man with longstanding type 1 diabetes developed major weight loss and marked deterioration in diabetic control. He had been persistently injecting insulin into areas of abdominal lipohypertrophy within which hard collagenised fibrous tissue nodules had developed. Injecting insulin at different sites dramatically improved blood glucose control. Fibrocollagenous nodules induced by insulin injections have not been previously described. Examination of a further 73 type 1 patients revealed lipohypertrophy in 44% and hard subcutaneous nodules on two

3. Jaeger C, Eckhard M, Brendel MD, Bretzel RG. Diagnostic algorithm and management of immune-mediated complications associated with subcutaneous insulin therapy. *Exp Clin Endocrinol Diabetes* 2004;112(8):416-21. PM:15372360

   Immune mediated complications associated with subcutaneous insulin therapy such as insulin neutralizing antibodies and/or skin reactions are rare conditions since human insulin is in general use. Nevertheless, if it occurs, a stepwise diagnostic approach is essential for differential diagnosis and consecutive treatment of these complications. Here we suggest a diagnostic algorithm to deal with e.g. insulin antibody formation of the IgG and/or IgE type and/or severe skin reactions resulting in poor metabolic control and often "brittle diabetes" in affected patients. This diagnostic algorithm includes step 1: Intradermal skin testing with positive and negative controls, additives and different insulin preparations; step 2: Quantification of insulin specific IgG and IgE in the serum, and step 3: Analysis of the time dependent binding/dissociation curves of the insulin neutralizing antibodies in an ex vivo/in vitro assay to assess the clinical significance of these antibodies. Based on 158 insulin treated control subjects and four patients with typical symptoms and signs representing the spectrum of immune-mediated complications subsequent to subcutaneous insulin therapy we demonstrate that the proposed stepwise approach leads to a definite diagnosis as a prerequisite for individual and successful therapy