Title of Project: Glycemic Variability in Subclinical Lipohypertrophy

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Study: Ultrasound detection of lipohypertrophy in patients with diabetes mellitus

Purpose: To determine if subclinical lipohypertrophy affects insulin absorption and glycemic parameters in patients with lipohypertrophy.

Hypothesis: Early hypertrophic changes in the composition of the subcutaneous layer of adipose tissue may be detectable via ultrasound and could alter insulin absorption.

Objectives: To determine the effect of subclinical lipohypertrophy on glycemic variability

Background:
Lipohypertrophy is a well-documented phenomenon in patients with diabetes in which hypertrophy and differentiation of adipocytes occurs in the dermal reticular layer at sites of subcutaneous insulin injection(1). Historically, lipohypertrophy was more common in type 1 diabetes prior to the development of purified recombinant human insulin, however it has been documented as a complication of newer insulin analogs in both type 1 and type 2 diabetes (2-4). Areas of hypertrophic nodules have decreased vascularity and are associated with poor glycemic control resulting in higher insulin requirements when used as a site of insulin administration (5). Conversely, if the site of injection is changed where insulin dosing has been increased, there is a risk of significant hypoglycemia as absorption can vary at non-hypertrophic sites (5-7). The detection of early, non-palpable lipohypertrophy remains difficult in the clinical setting. Recent studies have identified distinct ultrasonographic features of hyperechogenicity in areas of adipose tissue consistent with clinical evidence of lipohypertrophy at injection sites, and have detected changes in the thickness of subcutaneous tissue where not clinically evident in a population of patients with type 1 diabetes (8-10). Evaluation of insulin absorption at sites affected by clinically apparent lipohypertrophy through short-term continuous glucose monitoring has shown inconsistent results and it is yet unknown how or if subclinical lipohypertrophy affects absorption (11). In this study we propose to enroll at least 20 people who participated in phase 1 and who were determined to have subclinical lipohypertrophy to examine the correlation between

glycemic control and amount of insulin injected in subclinical hypertrophic areas using capillary blood glucose and continuous glucose monitoring.

Design, Specification of Endpoints, and Procedures:

Inclusion Criteria:

- **Participated in phase 1**
- **Determined to have subclinical lipohypertrophy**
- **Have had type 1 or type 2 diabetes for at least 2 years**
- **Currently using insulin to manage diabetes**
- **Have used insulin to manage diabetes for at least 2 years**
- **Age 19 or older**

Exclusion Criteria:

- **Taking insulin secretagogues (gliclazide, glyburide, glipizide) or other injectable medications (i.e. liraglutide/Victoza)**
- **Taking systemic steroids (e.g. prednisone)**
- **Not fluent in speaking and writing English (unless accompanied by a translator)**

In this second phase of the study, a minimum of 20 patients identified with subclinical lipohypertrophy in Phase 1 will be offered enrollment to assess glycemic correlation with injection in areas of subclinical lipohypertrophy. A separate enrollment and consent process will be undertaken by the diabetes nurse for this phase. Demographic information will be reviewed.

Patients will be randomized and data interpreters will be blinded to two alternating six-day protocols where the patients will be advised verbally and by written instruction to inject insulin in sites of subclinical lipohypertrophy or normal subcutaneous tissue. Patients will be asked to monitor and record their capillary blood glucose with meals and prior to bedtime using their own capillary blood glucose monitor. A trained research nurse at the Diabetes Centre will instrument each patient with an iPro 2 glucose sensor (Medtronic Canada). These sensors continuously measure blood glucose for periods of up to 7 days. A trained nurse will clean the skin with a superficial disinfectant and a small catheter will be inserted in the subcutaneous tissue at a non-lipohypertrophic site. The catheter will then be attached to a glucose sensor. Patients will wear this sensor for two periods of 6 days each at different sites. At the end of each of the two six day periods, the sensor will be removed.

Statistical Analysis:

In this phase of the study, we will measure the coefficient of variation of blood glucose during the different injection protocols. A student's paired t-test will be used to determine the difference if any in CV of glucose between injection sites.

Potential benefits:
Information gained from this study will expand the knowledge of the incidence of early hypertrophic changes, the ability to detect these changes using a novel ultrasound technique and the impact of these changes on glycemic control with insulin. Patients found to have hypertrophic changes will be advised to inject insulin at alternate sites and will be re-educated on the importance of injection site rotation. Patients with poor glycemic control may be able to improve their glycemic parameters or reduce their insulin dose should their requirements be due to insulin absorption issues at hypertrophic sites.

Risks:
There may be some discomfort associated with the insertion of the glucose sensor. There is a small risk of skin infection from the insertion of the glucose sensor and catheter and the possibility of an allergic reaction from the tape used to apply it. This risk occurs less than 1 in 1000 times the sensor is used. If patients have concerns regarding insulin dose adjustments they will have access to a diabetes education and research nurse who can assist with insulin dose titration. Any additional adverse events will be monitored by a trained research nurse at the Diabetes Centre.

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