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Lipohypertrophy and the Artificial Pancreas: Is This an Issue?

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It is well known that repeated injections of insulin in the same skin region by people with diabetes induce local reactions of the subcutaneous adipose layer, most often lipohypertrophy (LHT).[1,2] This also holds true for continuous subcutaneous insulin infusion (CSII) therapy in which the catheter of the insulin infusion set is frequently placed in the same locations, also conducive to LHTs.[3] A variety of studies indicate LHT is common—when it is sought—though with a range of prevalence reported (~16 to 60%).

Our knowledge about the impact of LHTs on insulin absorption is limited, not so much from a clinical point of view where it is quite obvious that the rate and amount of insulin absorption are reduced, in an often erratic manner, but from a scientific point of view, that is, we have only a quite limited number of systematic studies looking into the quantitative aspects of such changes in pharmacokinetics and pharmacodynamics (eg, by means of glucose clamp studies), most of them outdated or of insufficient quality.[4-7] It is perhaps surprising that the medical community, may it be clinicians, academic sites, insulin manufacturers or manufacturers of syringes/needles/pens, have not initiated well designed experimental studies addressing this practical, highly relevant issue in more detail given that LHTs are likely to be a major source of variability in glycemic control. If insulin administration is performed suboptimally, there may be little to gain from "intensifying" therapy by switching to insulin pumps and/or continuous glucose monitoring.

Our knowledge about factors triggering the subcutaneous tissue to develop firm growths of adipose tissue is also limited.[1,2,8,9] However, it appears this is the result of a multifactorial process, and that repeated injections/infusion with needles/catheters at the same body site in correlation with the insulin itself as a known growth promoter (insulin excipients might play a role as well) are important factors. With insulin injection, reuse of needles may increase local tissue trauma and hypertrophic responses.[1,8]

The success of artificial pancreas (AP) systems, which establish a closed-loop combining continuous glucose monitoring with insulin infusion, depends largely on consistent and preferably rapid insulin absorption and action; insulins with an ultra-fast absorption should enable a better AP performance but for the time being, we are restricted to the current rapid-acting insulin analogues, all with a Tmax of ~1 hour. Present AP prototypes need therefore carefully consider factors that may delay insulin absorption and/or increase its variability.[10] When an AP system starts to increase an insulin infusion triggered by a rise in glucose levels monitored, this infusion may not induce the desired decrease in glycemia (at least not at the time point intended) if the insulin is infused into an area of LHT, and if the AP system continues to increase the insulin infusion to prevent hyperglycemia, this may result in a considerable risk that the excess insulin applied induces hypoglycemia later. In addition, if the next infusion set (or injection for multiple daily injections) is applied in a non-LHT area where insulin uptake is faster and/or more complete, the risk of hypoglycemia may be increased, increasing the degree of glycemic variability.

Most AP systems currently under development require 2 skin punctures, 1 for the glucose sensor of the needle-type continuous glucose monitoring (CGM) system and 1 for the insulin infusion via a pump. Different attempts to combine glucose measurement and insulin infusion into 1 catheter, so called single-port systems, have made excellent progress in the last years; however, the first clinical trials with such systems have just started.[11] We have to assume that in the next several years the users of the AP systems will have to insert 2 "needles" over and over again. The need for 2 needles at the same time not only limits the skin areas that can be used further, it also limits the ability to rotate the insertion site to avoid generation of LHTs. This is of particular importance in young children.[3,8]

Another question is how much harm is induced to the skin/abdominal tissue by repeated insertions of the glucose sensor needle in the same site. Until now CGM insertion devices

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tend to be thicker than needles of the insulin infusion set. Clearly no insulin is infused at a sensor insertion site with today's systems; however, the insertion and subsequent movements of the sensor tip in the tissue while wearing the CGM system might not only induce acute local trauma and reactions but also run more chronic skin reactions especially if the same area is used for insulin application at other times. It is clear that the performance of the glucose sensor is influenced by the local reactions (biofouling) that are not well understood but determines the number of days sensor can be worn. To our knowledge reliability and accuracy of measurement when a glucose sensor tip is inserted into a LHT is, for all intents and purposes, unknown.

In addition, limited information is available about the actual location of the tip of today's CGM sensors when inserted—are they always in the subcutaneous adipose tissue? Or, might some be passing through the fat layer and into the muscle or muscle fascia beneath the adipose tissue? We know that average skin thickness at the common insulin injection sites is only 2.0-2.5 mm, with very few measurements above 3.0-3.2 mm. The SC fat thickness is much more variable.[12] When skin and adipose thicknesses are combined, the minimum total distance from skin surface to muscle (in a study population with a mean BMI of nearly 30 kg/m^2) was less than 5 mm at all 4 body sites commonly used for injection, including the abdomen which is overwhelmingly the most commonly used location for insulin pumps and CGM sensors.[13] It is unclear if this affects CGM performance.

The number of insulin infusion sets (IISs) required for continuous AP operation is higher than that of glucose sensors: The recommendation is to change the IIS every 2 to 3 days to avoid local inflammation and infection, as well as issues with insulin absorption at the insertion site that show up in most users after a few days, independent of the presence of LHTs. In contrast, glucose sensors may stay in place over 5 to 10 days or even longer. Per annum 120 to 180 IIS have to be inserted and 37 to 74 glucose sensors. As the diameter, length, and flexibility of the latter differ from that of the Teflon (or steel) IIS used (beside the fact that via the IIS insulin is infused), the local skin reactions induced are most probably different.

We argue that the real impact of LHTs on insulin absorption should be quantified to determine whether it is significant risk factor of real relevance for not only AP performance, but for common multiple daily insulin injection regimens, and CSII. Let's assume that LHTs have a statistically and clinically important impact on insulin absorption and insulin action. Sites used for insulin injection, and particularly insertion sites for the IIS (and probably the CGM needle) will require much more attention before AP systems are attached to the users in clinical studies and hopefully in the near future, when these become available as products for daily treatment of people with diabetes. Thus, it should be mandatory that the body sites intended to be used for the glucose sensor/IIS are examined carefully. LHT is often not visible, and diagnosed only by careful palpation. Users have to be made aware of the risks involved when they use sites with LHTs; they often use these out of habit, and come to prefer these sites as the pain associated with needle/catheter insertion is reduced. It may be also be of interest to evaluate AP performance when deliberately inserting the needles in skin areas with LHTs or avoiding these. This may highlight the relevance of LHTs for AP performance. Hopefully these comments will bring light to a clinically relevant aspect of AP system usage (and of insulin therapy in general) that may not have received the attention it may deserve. LHT is indeed an often overlooked bump in the road to consistent insulin therapy.

Abbreviations

AP, artificial pancreas; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; IIS, insulin infusion set; LHT, lipohypertrophy.

Declaration of Conflicting Interests

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