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COMMENTARY

Insulin Absorption from Lipodystrophic Areas: A (Neglected) Source of Trouble for Insulin Therapy?

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Abstract

The experienced clinical diabetologist first checks the skin at the area where the patient usually injects his insulin when he sees widely fluctuating blood glucose levels in the diary of the patient. He knows that insulin absorption from skin with lipodystrophic changes is irregular. However, our scientific knowledge about why this is the case is very limited. Most probably, the number of blood vessels near the insulin depot in the subcutaneous tissue varies depending on the nature of the lipodystrophic changes, or the structural changes in this tissue hamper the diffusion of insulin. Not only is our knowledge about the number of patients who exhibit such changes very limited, but also our understanding why such changes show up in certain patients and not in others is minimal. More practically important, we also have few quantitative studies investigating the impact of this diabetes-related complication on insulin absorption/insulin action; however, it is not difficult to run such studies in practice. Nevertheless, it is impressive to see how often metabolic control improves considerably once the patients apply the insulin into other skin areas.

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Insulin therapy relies on a reproducible absorption of insulin from the subcutaneous (SC) tissue. Application (injection or infusion) of insulin in a small skin area over and over again can induce lipodystrophic changes in skin structure, more precisely, not of the skin, but of the fatty tissue in the SC space. Such skin lesions are a complication of insulin therapy that is quite annoying for patients with diabetes, but mostly from an aesthetic/cosmetic point of view. In severe cases, liposuction was shown to be of help.[1]

It is a well-known fact that insulin application into such skin areas induces erratic insulin absorption, i.e., insulin is absorbed more rapidly or more slowly in comparison to other sites without such lesions in the same patients. This depends most probably on the kind of changes prevailing at the injection site: lipoatrophy or lipohypertrophy.[2] With insulin-induced lipoatrophy, absorption of insulin might be more rapid (and unpredictable) in comparison to normal skin, as the insulin molecules have a shorter distance to travel to hit a capillary. In case of advanced lipohypertrophy (which is the most commonly reported cutaneous complication of insulin therapy), the SC tissue is reported to be fibrous and relatively avascular. With a lack of blood vessels in the vicinity of the insulin depot, it is not surprising that the rate of insulin absorption—which depends on diffusion of insulin molecules across the endothelial barrier into the blood stream—is reduced. The size of lipohypertrophic skin changes can vary greatly in size and are often

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (SC) subcutaneous

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felt more easily than seen.[3] However, other types of skin alterations (e.g., nodular changes) have also been reported with unclear impact on insulin absorption.[4,5] Patients prefer to inject in such skin areas, as they are anesthetic, i.e., injection induces no pain.

What causes these local skin reactions? In the early decades of insulin therapy with highly impure insulin formulations, local skin reactions (reflecting local immunological reactions) were encountered by many, if not most, patients treated with insulin. Invention of highly purified insulin formulations ("monocomponent"), i.e., formulations that contain practically no other proteins, has reduced the incidence drastically. Also, introduction of human insulin has reduced the appearance of lipodystrophic skin lesions but not completely abolished them.[6] It appears that the injection technique, number of injections, reuse of injection needles, size of the injection area usually used, depth of insulin application, and other related factors (skin disinfection) also have an impact on the risk to develop such skin lesions.[3] With human insulin and insulin analogs, lipodystrophic skin lesions are probably induced by the insulin molecule itself (dimeric and hexameric insulin molecules can induce immunological reactions) or by excipients added to the insulin formulations. There is a close correlation between insulin antibodies and the appearance of lipodystrophic skin changes in children/adolescents.[7] It appears as if changes introduced to the insulin primary structure (i.e., insulin analogs) has a (beneficial) impact on the risk of developing such skin lesions. Some case reports (e.g., Roper and Bilous[8]) were published in which such skin lesions were reduced when patients switched from human insulin formulations to insulin analog formulations. It is not clear if this is due to the difference in the primary structure of the insulin molecule between the two insulin formulations or because the insulin analog is absorbed more rapidly, exposing the SC adipocytes for less time to the local lipogenic action of insulin. Nevertheless, diabetologists who see many patients day by day report that such skin reactions are still quite common. It appears as if the incidence of lipodystrophic skin lesions was never systematically studied with modern insulin formulations. Before the invention and widespread use of insulin analogs, lipohypertrophy was reported to occur in approximately 30% of all patients with type 1 diabetes (much less in patients with type 2 diabetes).[9] In a later survey, approximately 30% of >1000 patients checked had lipohypertrophy.[3] In close correlation with the typical injection sites, the sites at which such skin lesions show up was most often the abdomen. It appears as if the prevalence of lipoatrophy and lipohypertrophy is even higher in children/adolescents.[7] However, with modern insulin formulations, such skin changes were also reported; they can also show up with rapid-acting and long-acting insulin analogs.[10–14] So the question remains if this is a clinically relevant complication of insulin therapy or an issue with limited relevance.

The fact that the metabolic control of patients with lipodystrophic skin lesions is improved when they were instructed to apply the insulin into other sites is an indication of impaired insulin absorption from such sites.[15] Whether this automatically resulted in an improved overall metabolic control is questionable; at least, Hauner and colleagues[9] reported no significant differences in hemoglobin A1c between patients with and without lipohypertrophic skin lesions (also no difference in daily insulin requirements). However, it might very well be that the overall metabolic control is not impaired, but larger swings in glycemia take place due to unpredictable/altered insulin action (discussed later). But what do we really know from published studies about the impact of these skin lesions on insulin absorption/insulin action from a more scientific/quantitative point of view? A respective PubMed literature search revealed a very small number of hits about lipodystrophic skin changes and insulin absorption (e.g., Richardson and Kerr[2] and Johansson and associates[16]). In one clinical–experimental study, the absorption of a single SC dose of insulin aspart was studied when administered to lipohypertrophic tissue in nine male patients with type 1 diabetes.[16] Selection of subjects was based on the detection of a visible, palpable, and massive thickening of fat tissue with higher consistency and grade of lipohypertrophy at the site of injection. On the two study days, patients received SC injections of 10 U insulin aspart in the abdominal wall by a diabetes nurse prior to a standardized breakfast. A higher C_{max} of plasma insulin was observed after injection in normal tissue (226 ± 32 pmol/liter) than in lipohypertrophic tissue (169 ± 33 pmol/liter; $p < .015$), with higher insulin levels recorded between 40 and 90 min after injection. The area under the curve, 0–240 min, was 294 ± 36 (normal tissue) versus 230 ± 39 (lipohypertrophic tissue) ($p < .051$). Thus absorption of insulin aspart was impaired in lipohypertrophic tissue, yielding a 25% lower C_{max} of plasma insulin. Johansson and associates[16] speculate whether local degradation of insulin takes place in lipohypertrophic tissue to such an extent as to explain the observed differences in plasma insulin profiles. However, it appears as if no systematic and appropriate pharmacodynamic studies about this question have

been published, at least, not since 1995 and not in journals that are listed in PubMed. Also, the number of older publications about this topic is quite small, as revealed by contacting a number of experts in insulin pharmacology and checking older review articles about insulin therapy. Many of the older studies use inappropriate methodology to quantify the effect of skin lesions on insulin absorption or studied insulin formulations that are no longer being used.[17,18] So one can summarize that there is a considerable number of articles about lipodystrophic skin lesions in patients with diabetes—most often case reports—per se, but there is a very limited number of systematic pharmacokinetic (and no pharmacodynamic) studies about the impact of such skin changes on insulin absorption/insulin action.

One reason for this lack of knowledge can be that it is difficult to study the impact of lipodystrophic skin lesions on insulin absorption properties. Clearly, recruitment of such patients might require more efforts than for other studies; however, this is not a fundamental hurdle as each specialized diabetes practice has a number of such patients. As such patients might present themselves with a range of lipodystrophic changes, proper classification of these individual skin changes is an issue; however, by means of modern ultrasound methods, they can be relatively precisely characterized. Most probably, it would be a good starting point to perform a euglycemic glucose clamp study with 10 or 20 patients with, e.g., lipohypertrophy. On one study day, the insulin (e.g., a rapid-acting insulin analog) would be injected (or infused) into a skin area with such changes, and on another day, in a nearby skin area without these changes. In view of the potential differences between patients, depending on the nature of the individual lipodystrophic changes, it would be advisable to show all individual profiles obtained and not only an average curve. This would enable better interpretation of the obtained responses, which might differ considerably. In order to also evaluate the clinically important aspect of intra-individual variability, it would be ideal if these experiments were repeated with injection of the same dose and type of insulin in the same injection site at least twice (i.e., four experiments in total).

Such a study would provide information about the absorption properties of injected insulin, but not about insulin that is infused continuously into the SC tissue (continuous subcutaneous insulin infusion [CSII]). It also appears as if there are no data available describing if lipodystrophic skin lesions took place more often in patients on CSII in comparison to those with SC injection therapy (with the same insulin formulation, etc.).[13] The fact that, with CSII, the local insulin levels around the tip of the catheter are high in the SC tissue for up to several days (depending on the duration of the catheter usage) might have an impact on the risk to develop lipodystrophic skin lesions. Also, the number of potential skin sites for catheter insertion (depending on the place where the pump itself is usually fixed, practical to handle, and the catheter length/visibility) is lower than with SC injection, which, in turn, increases the risk to develop such skin changes. In addition, CSII itself carries the risk of abscess formation and scarring due to prolonged usage of catheters that penetrate the skin.

Clearly, not only are the absorption properties of prandial insulin impaired if the insulin is injected into lipodystrophic skin areas, but also those of basal insulin are affected. In one of the very few studies about this topic, it was reported that the absorption of neutral protamine Hagedorn insulin for palpable abnormal injection sites is reduced.[19]

It is somewhat worrisome to see how many practically relevant aspects of insulin therapy receive relatively little or no interest. It is tempting to speculate why only a few scientists/diabetologists—and no company—have invested time and money in studying this topic. One might say it is relatively easy to overcome this issue by advising the patients to rotate the application site for their insulin appropriately. In one survey with >1000 patients, performed in Europe some years ago, less than 50% of the patients reported that they were taught about lipohypertrophy.[3] Therefore, more attention should be paid to this topic not only during teaching and training programs for patients but also during patient visits to the clinic, injections sites should be inspected carefully by nurses and physicians, especially in those with erratic glycemic control.[15] As the skin lesions are not always visible, sites should be palpated rather than just visually examined. It appears as though, even when respective advice was given, this had limited success in at least a subset of the patients who would stick to their usual habits. Probably, it will convince these patients if we can show them the impact their behavior has on the metabolic effect of the applied insulin (might it be a reduced metabolic effect in general or a relevant shift in the timing of the metabolic effect). We simply do not know the number of patients whose bad metabolic control is the consequence of applying the insulin in skin areas from which the insulin is not absorbed properly. Usually, such "uncooperative patients" (which every diabetologist has) are blamed for not doing what they

are supposed to do. However, there is probably at least some rational explanation to such treatment resistance if these patients have lipodystrophic skin changes that nobody is aware of or that are not regarded as relevant for good metabolic control. By means of continuous glucose monitoring, it should be possible to demonstrate to patients how many of the swings in their daily blood glucose profile can be reduced by simply injecting into other skin areas.[20] This would also be an approach for clinical studies to investigate the practical relevance of such skin lesions and to evaluate quantitatively measures taken to counteract this factor. Probably, patients with severe forms of such skin lesions are the ones who would greatly benefit from changing the route of insulin administration, e.g., applying the insulin by the pulmonary route.

One can envision that, with a relatively small set of clinical and clinical–experimental studies, our knowledge about this complication of insulin therapy would be expanded drastically, and we would have a much clearer view on the relevance of this insulin treatment-related complication.

Disclosure:

The author is a consultant for a number of companies that develop novel diagnostic and therapeutic options for diabetes treatment.

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