The metabolism of the diabetic foot

In vivo investigation with microdialysis

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Submitted 02-09-23. Accepted 03-05-07

Background **Many amputations might be delayed or prevented by more effective clinical supervision of the diabetic foot ulcer. The aim of this study was to measure the local metabolism on the edge of a diabetic ulcer and compare it to healthy subcutaneous tissue.**

Patients and methods **In 5 non-fasting diabetic patients, we inserted a microdialysis catheter into the edge of a diabetic ulcer and a reference catheter into healthy abdominal subcutaneous tissue, and recorded the local concentrations of glucose, lactate and glycerol during rest.**

Results **The concentrations of glucose in the ulcers were 7.8 mM (SEM 1.9) and in the reference tissue 10.6 mM (SEM 1.8) (p = 0.4). The concentrations of lactate were 2.9 mM (SEM 0.7) and 2.1 mM (SEM 0.7) (p = 0.2), while those of glycerol were 290 μM (SEM 84) vs 98 μM (SEM 7.2) (p = 0.002).**

Interpretation **This study shows that microdialysis can detect differences in dialysate concentrations of metabolites in diabetic ulcers and a reference tissue, providing valuable information concerning metabolites in the diabetic foot ulcer. Future studies should combine the technique with measurements of local blood flow.**

Neuropathy, vascular diseases and infections are associated with diabetes mellitus and ulceration of the foot is one of the feared complications. The important prelude to successful treatment of the ulcer is the differentiation between these main syndromes (Gentry 1993). Knowledge concerning the local metabolism of diabetic ulcers is scarce (Simonsen et al. 1998). Microdialysis was first developed for the study of glucose metabolism in brain tissue. With this technique, it is possible to monitor interstitial changes of glycerol, glucose and lactate in various tissues under clinical conditions (Benveniste and Huttemeier 1990). We investigated the interstitial concentrations of glucose, lactate and glycerol at the edge of a diabetic ulceration and compared these to a healthy reference tissue.

Patients and methods

5 non-fasting diabetic patients (3 men) with a unilateral chronic foot ulcer were included in the study. 3 patients had non-insulin-dependent and 2 had insulin-dependent diabetes mellitus. Their median age was 53 (35–74) years and the median duration of the disease was 20 (8–54) years. All patients had had a diabetic ulcer for more than 6 months. They had normal toe blood pressure and 4 patients had a palpable posterior tibial artery pulse. The ulcers were located distally on the dorsal or plantar aspect of the feet. 3 of the patients had neuropathy. At the time of the study, none of them had ulcers that were infected or needed surgical revision. The median follow-up after the study was 7 (2–7) months. 5 months after dialysis, 2 patients developed an infection and underwent surgery. *S. aureus* and *B. fragilis* were found in the ulcers. After local application of 1 mL lidocaine, a microdialysis catheter was inserted into the edge of the ulcer, and a reference catheter was inserted into healthy abdominal sub-

cutaneous tissue. After 1 hour of calibration, the local tissue concentrations of glucose, lactate and glycerol were recorded over a period of one hour with the patient resting.

The microdialysis technique, as in dialysis, uses a membrane permeable to water and small solutes. It is continuously flushed and a concentration gradient is created, causing the diffusion of solutes from the interstitial space into the dialysis. Samples are taken in microvials and analyzed (Benveniste and Huttemeier 1990). We used CMA 60 catheters (Microdialysis A/B, Sweden, membrane length 30 mm with a molecular cut-off at 20 kDa). The catheter was flushed with Ringer's chloride (Microdialysis A/B, Sweden, Na^+ 147 mM, K^+ 1.4 mM, Ca^{2+} 2.3 mM, Cl^- 156 mM, pH 6, osmolarity 290 mosmol/kg). The flow rate of the microdialysis system was 0.3 μL/min (Microdialysis A/B, Sweden, CMA 106). Under these conditions, the relative recovery of the metabolites measured is about 90–100% (Ederoth et al. 2002). We analyzed the concentrations of glucose, lactate and glycerol, using a CMA 600 Drug Analyzer (Microdialysis A/B, Sweden). The mean values (SEM) are given.

All data were compared, using a rank sum test. P-values < 0.05 were considered significant.

The local ethics committee approved the study. The subjects gave informed consent before participating in the study.

Results

The interstitial glucose concentrations in the ulcer area were 7.8 mM (SEM 1.9) vs. 10.6 mM (SEM 1.8) in the reference tissue (p = 0.4). The lactate concentrations were 2.9 mM (SEM 0.7) and 2.1 mM (SEM 0.7), respectively (p = 0.2). The interstitial concentrations of glycerol in the ulcers were 290 μM (SEM 84) vs. in reference tissue 98 μM (SEM 7.2) (p = 0.002). The blood glucose was 11.8 mM (SEM 2.7) in the diabetic ulcer and similar to that in the reference tissue (p = 0.8) (p = 0.3). The ratio of glucose measured in healthy abdominal subcutaneous tissue to that in the ulcer was 1.6 (SEM 0.24), while the ratios for lactate and glycerol were 0.73 (SEM 0.12) and 0.46 (SEM 0.13).

Discussion

Microdialysis has been used to monitor metabolic and inflammatory parameters in bone and tendon (Thorsen et al. 1996, Langberg et al. 2002). We measured glucose and lactate levels because they give information about the substrate, availability and redox state of the tissue. In one study, lower concentrations of glucose and higher concentrations of lactate were found in chronic diabetic foot ulcers than in reference tissue (Simonsen et al. 1998). Unfortunately, the interstitial concentrations of glycerol in the diabetic foot ulcers were not measured. Glycerol is an important metabolite and seems to be of clinical interest. It reflects the degradation of glycerol phospholipids in cell membranes, because it is an end product of membrane phospholipid degradation (Hillered et al. 1998). Studies using microdialysis in ischemic tissue have shown higher concentrations of glycerol (Sarrafzedeh et al. 2002, Stahl et al. 2001). The interstitial concentrations of local metabolites can be affected by several factors—e.g., blood flow and hormones. As regards glycerol, an increase in local blood flow increases the transport of this compound away from the tissue, but it increases the transport of glucose to the tissue (Ederoth et al. 2002). Our study showed higher concentrations of glycerol and similar levels of glucose and lactate in the ulcers. The sympathetic tone increases during surgical stress and lipolysis is promoted (Udesen et al. 2000). However, this universal response cause higher concentrations of glycerol in both the ulcer and reference tissue. Studies that include measurements of blood flow and hormones may contribute to the search for mechanisms underlying the metabolic values. We included ulcers that showed no clinical sign of ischemia or infection and used the abdominal subcutaneous tissue as reference tissue. No large difference in dialysate concentrations was expected. The contralateral foot might have been better as a reference tissue, but the risk of causing an ulcer, even by a minor trauma, prevented us from using it. Our small sample size precludes a detailed analysis, but it is noteworthy that two of the diabetic patients with high local interstitial concentrations of glycerol had an unfavorable outcome—i.e., they needed surgical revision of their ulceration. Indeed, the high concentration of glyc-

erol that we found may have predicted the clinical outcome. This study shows that microdialysis can detect differences in dialysate concentrations of metabolites from diabetic ulcers and a reference tissue. In combination with measurements of local blood flow, microdialysis can give valuable information concerning local metabolism in the diabetic foot ulcer. Further investigations are needed to ensure proper care of the diabetic foot, which may predict inflammation and necrosis.

We thank the Johs. M. Klein & Hustrus Mindelegat and Alice & Tage Sørensens Fond for the support of this study.

No competing interests declared.

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