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Treatment of Diabetic Foot Syndrome By Means of Hyaluronidase Infusion Therapy – Single Patient Case Report

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ABSTRACT

Background: *Diabetic foot syndrome (DFS) is one of the most severe secondary complications of diabetes mellitus. It is currently treated with improvement and maintenance of good glycemic control, pain drugs, antibiotics, and drugs and surgical measures to improve the vascular blood flow into the legs. In late stages, foot amputation (in part or total) is the only means to safe the patient's life.*

Case Report: *A 56-year-old woman with type 1 diabetes for more than 40 years, suffered from diabetic foot syndrome with complete closure of the arteria fibularis and a non-healing foot ulcer at the left leg. The need for lower ankle amputation was already determined. We tried to improve the vascular situation by means of a series of intravenous hyaluronidase infusions over a period of three weeks. An immediate improvement of the general condition was observed. The ulcer healed completely within 8 weeks, and a re-opening of the previously closed vessel as well as further additional collateral blood-flow into the left foot could be determined by means of an angiogram six months later.*

Discussion: *The observed beneficial impact of intravenous hyaluronidase treatment on atherosclerotic lesions can be explained by the molecular action of the enzyme on the glycocalix, the extracellular hyaluronan layer that separates the endothelial cells from the blood stream. Successful treatment of DFS with hyaluronidase infusions has been reported already 50 years ago but research on this topic ceased, when stents and other apparently more compelling vascular treatment methods were detected.*

Conclusions: *In a severe case of DFS, we were able to re-open a critical arterial vessel and improve the entire vascular blood flow by means of intravenous hyaluronidase infusions. Clinical studies are required to confirm the value of hyaluronidase infusions as treatment alternative to amputation for DFS.*

Keywords

Diabetes mellitus, Diabetic foot syndrome, Foot ulcer, Vascular occlusion, Atherosclerosis, Hyaluronidase, Neuropathy.

Introduction

Diabetic foot ulcers are the most common precursors of amputation and an important cause of morbidity and mortality in patients with diabetes [1,2]. Major part of the healthcare costs related to diabetes treatment in the UK are spent on hospitalizations related to diabetic foot syndrome (DFS) [3]. The pathophysiology of DFS includes vasculopathic and neuropathic complications of diabetes [4]. A prevalence of 3% to 30% among patients with diabetes has been reported in the literature [5]. Between 10% and 30% of patients with DFS develop ulcers, which increases the risk of amputation by 8- to 23-fold and substantially increases mortality [6-8]. Even today a lower limb is lost every 20-30 seconds due to diabetes

somewhere in the world [9,10].

DFS pathophysiology is based on several etiological factors: peripheral neuropathy, peripheral arterial disease, infection, and trauma, e.g. induced by the use of inappropriate shoes [11]. Next to peripheral neuropathy, peripheral arterial disease is another major risk factor for diabetic foot syndrome. Peripheral arterial disease leads to impaired wound healing and may require lower extremity amputation. If both deteriorations are present, a minor trauma, e.g. caused by inappropriate shoes or by an acute injury, can result in a chronic ulcer [10,11]. The foot ulcers observed under such conditions can present with differing severity and may reach a remarkable size and depth [11-14].

Treatment of DFS includes efforts to improve and maintain good glycemic control [15] and clinical and surgical measures to achieve revascularization [15,16]. If this is not possible, gene- and stem-cell therapy, hyperbaric oxygen, sympathectomy, spinal cord stimulation, prostanoids and other interventions have been recommended. However, it is commonly accepted that appropriate wound care and strict offloading may be the only effective maintenance therapy and that timely amputation is required to accelerate mobilization and improve the quality of life [16]. However, foot amputation is a substantial event and has a major impact on the life of the affected patient.

It may therefore be worthwhile to investigate other interventions, which have the potential to interfere in a beneficial way with the pathophysiology of atherosclerosis and DSF. It has been reported that glycocalyx damage is a key pathologic step in a diverse array of clinical conditions, including diabetic complications, sepsis, preeclampsia, and atherosclerosis [17]. Changes to the endothelial glycocalyx (reduction in thickness and surface coverage) are one of the earliest detectable vascular changes in the course of diabetes [18]. It is tempting to speculate that remodulation of the glycocalyx by exposure to hyaluronidase leading to improved functionality of the hyaluronan layer may be a potential effective treatment alternative [19,20]. In animal experiments, exposure of atherosclerotic tissues with plaque lesions to bacterial hyaluronidase resulted in fast and effective degradation of the plaques [21]. In experimental studies and anecdotal clinical cases, it has been demonstrated that atherosclerotic plaques can be reduced or even removed by the i.v. administration of high doses of hyaluronidase in patients with coronary heart disease and/or arterial obstructive disease resulting in improved vascular function [20-24]. Already fourty years ago, intra-arterial administration of hyaluronidase was used to effectively treat severe cases of diabetic foot syndrome and to avoid limb amputation [25]. However, invention of stents and other effective surgical means of re-vascularization might have been the reason why further research on this topic was not conducted.

Here we report on a single case, where severe DFS could be effectively treated by means of a series of intravenous infusions of bovine hyaluronidase.

Patient Case Report

The patient was a 56 year-old woman with type 1 diabetes for more than 40 years. She was on intensive insulin treatment since manifestation but because of panic fear for hypoglycemia, she treated herself constantly in a hyperglycemic range (HbA1c: 10.9 %). She had peripheral neuropathy for more than five years, and a non-healing chronic ulcer had occurred below the left heel for more than two years (Figure 1a). A complete occlusion of the arteria fibularis posterior was detected in an angiogram three months prior to the intervention (see Figure 2a). There were no palpable foot pulses, and no blood flow could be detected by laser doppler fluxmetry. Based in these findings, amputation of the lower left food was considered as the only remaining option to improve the prognosis of the patient. As a last resort and supported by prior clinical results [21,22], an attempt to improve the disastrous condition by means of intravenous application of hyaluronidase (experimental off-label use approach).

The employed hyaluronidase product is approved for arthritis treatment and several other indications in Germany (Hylase-Dessau, Riemser Pharma). In this case, a series of ten intravenous infusions every second day was made (15,000 U of hyaluronidase in physiological sodium chloride solution by means of an infusion pump within 60 min). This dose is a three times higher dose than normally employed for other indications and was chosen based on previous experience and to enhance anti-inflammatory efficacy. The patient gave explicit written informed approval for this experimental treatment and each infusion was monitored with continuous pulse and blood pressure surveillance.

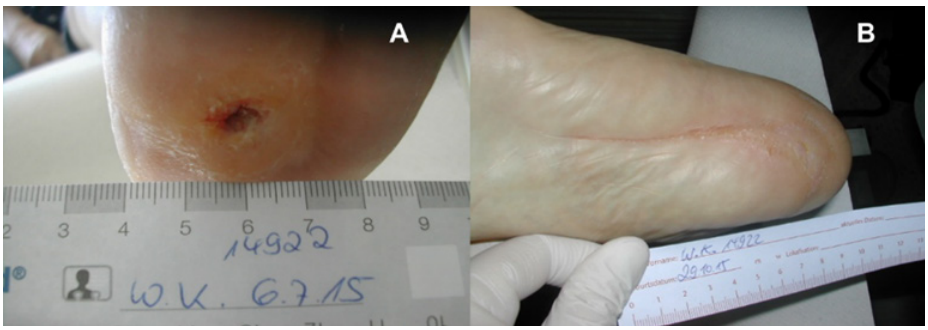

Figure 1: Picture of the chronic diabetic foot ulcer at the left heel before (A) and picture of the skin at the left heel (B) three months after the hyaluronidase intervention.

All individual treatment procedures were very well tolerated, and no adverse event was reported during the entire treatment period. After the first infusion, the patient reported about a substantial general improvement of her well-being, which was maintained throughout the entire subsequent treatment procedures. In parallel, the patient underwent a structured diabetes training.

It is anticipated that the hyaluronidase infusions induce a broader glycocalyx remodulation, which continues for a subsequent period of several weeks and months. The ulcer healed completely within the next three months (Figure 1b). In the angiogram after 6 months, which was performed by the same radiologist who conducted the previous examination, a re-opening of the arteria fibularis was observed (Figure 2b). Foot pulses were palpable and substantial blood-flow was measured by laser-doppler fluxmetry. The planned amputation was cancelled, and the patient continued with her normal life and with better glycemic control (HbA1c after 6 months 7.5%) and with a good prognosis to keep her leg (so far for 7 years).

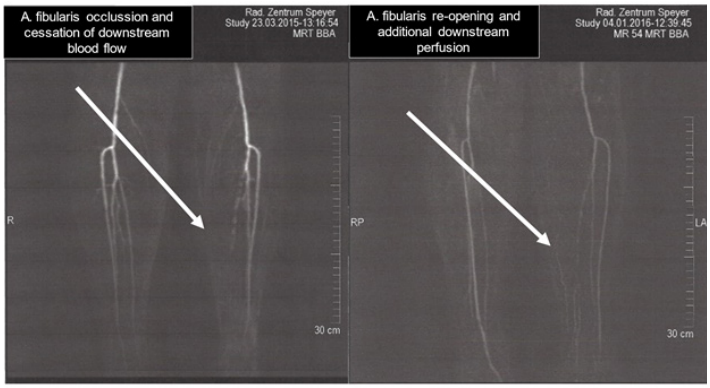

Figure 2: Angiogram of the lower extremities before (A) and 6 months after the hyaluronidase intervention. Re-opening of the left arteria fibularis and additional perfusion of the lower left foot can be observed as treatment result.

Discussion

Hyaluronan (the macromolecule of hyaluronic acid, HA) is a large, non-sulfated glycosaminoglycan that is ubiquitously present in the extra-cellular matrix of all vertebrates in high-molecular form. During inflammation and tissue injury, e.g. in atherosclerosis, low-molecular-weight fragments are predominantly built, which exert angiogenic and pro-inflammatory effects [26,27]. Hyaluronan is a dynamic molecule and a with turnover rate of 5 g/day of the total 15g in the body, it has a high rate of metabolism [28]. The majority of the hyaluronan in the vasculature is incorporated into the endothelial glycocalyx and the extracellular matrix of the underlying tissue [20,29-31]. Glycocalix composition and hyaluronan content play a major role in the permeability of the layer. Treatment with hyaluronidase has been shown to increase permeability in post-capillary venules in the rat [30]. In consequence, remodeling of the HA content of the glycocalix in favor of high-molecular weight isoforms may be a therapeutic target for treatment of atherosclerosis and diabetic foot syndrome [20].

Treatment of the vasculature with intravenous hyaluronidase may result in the rapid formation of a new and less damaged glycocalyx composed of high-molecular weight hyaluronan in patients with chronic system inflammation. During the infusions, the enhanced permeability after i.v. administration allows the enzyme to penetrate into the smooth muscle cell layer. The hyaluronidase molecules may reach the plaques, where hyaluronan is also present as one of the major skeletal components of the plaque itself [32-35]. After cleaving the solid proteoglycans, the plaque may become more flexible and may better be targeted and dissolved by further self-repair mechanisms within the arterial wall. Fast and effective degradation of the plaques was observed in animal experiments after exposure of atherosclerotic tissues with plaque lesions to bacterial hyaluronidase [21]. Others and we observed measurable reductions of atherosclerotic lesions in individual patients with coronary heart disease or peripheral occlusive artery disease [22-24]. Beneficial impact of intravenous hyaluronidase treatment on atherosclerotic lesions has been reported already 40-50 years ago [25,36,37] and can be explained by the molecular action of the enzyme. It may hence be worthwhile to investigate hyaluronidase infusions in combination with improved glycemic control as treatment for late-stage diabetic foot syndrome and as alternative to amputation.

Conclusions

Intravenous treatment with hyaluronidase resulted in re-vascularization of the left leg in a patient with severe diabetic food syndrome. Instead of undergoing amputation, the patient could keep the leg with a good prognosis for the years to come. Controlled clinical studies are warranted to verify and confirm the combined effect of intravenous hyaluronidase and improved glycemic control on diabetic foot syndrome.

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