

Diabetic Ulcers: Microcirculatory Improvement and Faster Healing with Pycnogenol

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Summary: Diabetic microangiopathy leads to lower limb ulcers that are very slow to heal. Pycnogenol was evaluated on diabetic ulcers in a controlled trial. Ulcer medications were used in 4 groups of 30 patients: (1) systemic Pycnogenol and local application; (2) local Pycnogenol only; (3) oral Pycnogenol; and (4) medications only (control group). Ulcerated areas and symptom scores were more reduced with the combined oral and local treatment ($P < .05$). Oral and local treatment were less effective, but still improved compared with the controls. Combined

treatment produced 89% complete healing at 6 weeks versus 84% with local treatment and 85% with oral treatment; healing in controls was 61%. The combined treatment group and oral only group had better microcirculation after the combined treatment. Combined local and systemic application of Pycnogenol may offer a new treatment of diabetic ulcers. Local treatment also speeds ulcer healing.

Keywords: diabetic microangiopathy; Pycnogenol; capillary filtration.

Diabetic microangiopathy (DM) and foot ulcerations are often the consequence of a complex clinical picture involving neuropathy, infections, postural problems, decreased arterial perfusion edema, and an impaired healing capacity, particularly, of the tissues of the foot, which is continuously traumatized.¹⁻⁷ Diabetic microangiopathy can be defined as a *high-perfusion microangiopathy*, comparable with chronic venous insufficiency (CVI) and generally characterized by the presence of edema.¹⁻¹¹

Chronic alterations in capillary perfusion and pressure and the progressive, early-for-age atherosclerotic changes in major arteries associated with diabetes result in perfusion disease and cause

severe microangiopathy that can eventually lead to ulcerations and amputations.¹⁰⁻¹⁸ The most important factors associated with the development of microvascular alterations in DM are the increase in capillary perfusion and distal edema, particularly when the patient is standing. Stasis, as a result of reduced or altered mobility, chronically increases the pressure in the capillary system even more, causing further edema and ulcers.³⁻¹²

Diabetic microangiopathy and venous hypertensive microangiopathy⁸⁻¹⁶ are characterized by increased skin flux at rest (flux is the flow measured by laser Doppler flowmetry), by an irregular alteration of the venoarteriolar response, namely the axon reflex producing vasoconstriction when passing from the supine to the standing position,¹²⁻¹⁷ by other dynamic laser Doppler alterations, and by a decrease in skin P_{O_2} associated with an increased skin P_{CO_2} .¹² These parameters are linked to a measurable increase in capillary filtration, clinically evident as edema, which may be measured by strain gauge plethysmography. The control of local edema is the key to control the microcirculatory changes in both DM and CVI.¹⁶⁻²¹

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Pycnogenol (Horphag Research Ltd, Guernsey, UK), a standardized extract from the bark of the French maritime pine, combines antidiabetic effects with improvement of signs of CVI. Pycnogenol reduced dose-dependently fasting and postprandial glucose levels in type II diabetic patients²² and improved glucose and HbA_{1c} levels of diabetic patients in a double blind, placebo-controlled study.²³ Pycnogenol controls increased permeability of altered capillary walls, prevents edema, and has several anti-inflammatory actions that contribute to the improvement of venous hypertension and venous microangiopathy.²⁴⁻²⁶ An inhibition of platelet aggregation²⁷ and an improvement of microcirculatory parameters have been shown in clinical studies.²⁸

Aim of this pilot study was to evaluate the healing power of Pycnogenol after oral or a combined oral and topical application on diabetic ulcers compared with a control group receiving only local ulcer care without Pycnogenol. The influence on microcirculation and on symptoms was another target of our investigation.

PATIENTS AND METHODS

Inclusion Criteria

The definition of diabetic microangiopathy and its assessment with neurophysiologic methods and by laser-Doppler measurements have been previously discussed.¹⁻²¹

The study included diabetic patients (treated with insulin) with severe microangiopathy causing foot ulcerations, who had tibial arteries with flow that could be documented by Doppler and a peripheral tibial pressure exceeding 60 mm Hg; however, because of calcification of the peripheral arteries, this kind of pressure is not very reliable in diabetic patients.

Laser Doppler skin perfusion pressure (SPP) was on average more than 50 mm Hg at the foot. Therefore, the ulceration was a combination of neurologic disease, trauma, edema, and infection, and was only minimally caused by decreased peripheral perfusion.

Color duplex imaging had also indicated that no patients had severe stenosis or obstruction at the femoral/iliac artery level or recent venous thrombosis.³⁻²⁰ Diabetic ulcerations had been present in their clinical history for the first time and the lesion had been present for at least 2 months.

Exclusion Criteria

Exclusion criteria were any clinical disease requiring treatment, severe bone or joint problems or limited mobility, uncontrolled diabetes, severe hypertension, signs of systemic infections, obesity, recent thrombosis (<6 months), and the presence of aneurysms or thrombi.

Exercise Plan

An exercise plan was presented to all included subjects by an educational video explaining the problems causing foot ulcerations in diabetic patients, particularly stressing foot protection. Friction-free socks (Sanagens, Treviso, Italy) were used to protect the foot and keep the medications in place during the study period.

Treatment.

Patients were randomly assigned to four groups. Group 1 participants received 150 mg/d Pycnogenol in capsules (50 mg, 3 times daily) as oral treatment and 100 mg Pycnogenol from capsules as powder placed on the ulcerated area (Table 1). Group 2 patients received oral treatment with 150 mg/day (50 mg, 3 times daily). Group 3 received only local treatment (100 mg) on the ulcer. Group 4 received no medical treatment, but ulcer care as the other subjects.

The ulcerated area was carefully washed and cleaned with warm water and a diluted, mild local disinfectant (Citrosil, Esoform, Italy). Ulcers were dried with paper tissue. Patients in the groups using local treatment received powder from 2 capsules (100 mg Pycnogenol) as a fine layer dispersed on the ulcer area. Treatment for all patients continued by placing a soft paper, nonallergic dressing over the ulcer and applying a layer of Tensoplast (BSN Medical, Pinetown, South Africa) elastic-adhesive bandage. Ulcers were washed and medicated every day for 6 weeks.

The area of ulceration was copied on a transparent plastic sheet, and the relative integral of the area recorded in a computerized Logitech (Palo Alto, Calif) system. The areas at inclusion and at 6 weeks were measured with the same technique.

A microcirculatory evaluation was performed at inclusion and repeated after 6 weeks. Because of the complexity and costs, microcirculatory measurements were performed in the group receiving

TABLE 1. Details of Study Subjects^a

	Pycno Oral+ Local	Pycno Local Only	Pycno Oral Only	Controls
Patients (n)	8	8	6	8
Age	54.3 (4.4)	55 (5)	55 (3)	52.4 (6.1)
Male:female	3:5	3:5	4:2	4:4
Duration of disease (years)	11.3 (2.6)	11(2.4)	11.2 (4)	12 (3)
Skin perfusion pressure (mm Hg)	>68 (5)	>66 (5)	>65 (6)	>65 (7)

a. There were no differences among groups at inclusion. Data in parenthesis is the standard deviation. *P* was not significant for all data.

Pycnogenol as combined oral and local treatment, in the group receiving only oral Pycnogenol, and in control group.

Transcutaneous PO_2 and Pco_2 were measured with a combined measurement (CombiSensor, Kontron, UK) after heating the skin to 44°C. Measurements were recorded after a period of 20 minutes of stabilization and capillarization of the area.

Microcirculatory measurements were made at 1 cm away from the ulcer edge, in noninflamed or infected area where the skin was intact.

In the area of microangiopathy surrounding diabetic ulcerations, an increase in skin Pco_2 is considered as a negative factor indicating lower and altered perfusion. This is usually associated with a significant fall in skin PO_2 indicating a decreased level of oxygenation and slower, less efficient perfusion leading to slow healing. The target, to improve microcirculation is to increase skin PO_2 and lower Pco_2 at the same time.

Edema is the hallmark of diabetic microangiopathy, and any high-perfusion microangiopathy, and for this reason the control of edema tends to improve healing and to make it faster.

Laser Doppler Evaluation

In diabetic microangiopathy, a number of microcirculatory alterations may be observed, measured, and monitored. Skin flux at rest is generally increased in the skin of diabetic patients with microangiopathy. The venoarteriolar response, the vasoconstriction observed when passing from the supine to the standing position, is generally impaired. The failure in venoarteriolar response owing to neuropathy and microangiopathy-limiting capillary pressure on standing results in an absence of the vasoconstrictive, protective action

on capillaries. This leaves more capillary loops open to exchange, with consequent extrafiltration of water in the extracapillary, interstitial compartment. More open capillaries and more segments of capillary loops open to circulation increase exponentially the exchange surface, therefore increasing both skin temperature and extrafiltration, particularly of water and of lighter protein. This starts a chain reaction with several events, including a much higher osmotic pressure in the extracapillary compartment that results in severe edema. At one stage, also due to the neuropathy, the capillaries seem to have lost the capacity of reacting by constriction, therefore aggravating edema even more.

Score

The evaluation of the microcirculation was also performed by an evaluation of a clinical score referring to signs/symptoms where 0 indicated absence of symptoms and 10 was very severe signs/symptoms. The score was recorded at the beginning and at the end of the study. However, the presence of signs/symptoms, particularly pain, owing to the severe neuropathy is generally highly variable in these subjects. Actually, anesthesia in the affected area may result in completely asymptomatic ulcerations.

Pycnogenol is a natural blend of constant proportions of bioflavonoids including catechin, epicatechin, taxifolin, oligomeric proanthocyanidins, and phenolic acids, as ferulic acid and caffeic acid. Clinical studies in thousand of patients have shown, very rarely, in a very limited number of subjects, only very mild, temporary side effects.²⁴

In this study, direct questioning was used to evaluate tolerability and compliance, particularly gastrointestinal problems, systemic and local skin

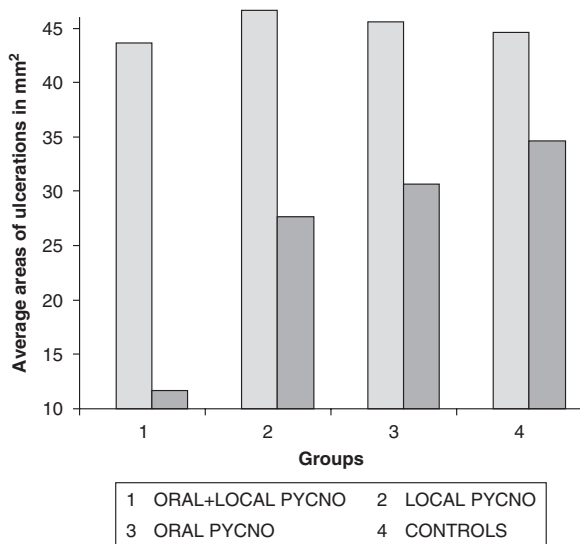
TABLE 2. Results: Average Ulcerated Areas at Inclusion and After 6 Weeks of Treatment

	Week	Pycno Oral+ Local	Pycno Local Only	Pycno Oral Only	Controls
Ulcer area (mm ²)	0	43(4)	46(6)	45 (4)	44 (5.2)
	6	11 (4) ^{***†}	27 (7) ^{**}	30 (6) [*]	34 (5) [*]
Symptom score	0	7 (3)	7.1 (3)	7.2 (2.2)	7.1 (2)
	6	2.2 (2) ^{***†}	4 (2) ns	3.8 (2.2) [*]	5.1 (3)
Healing (%)		89 [*]	84 [*]	85 [*]	61

Symptom scores: 0 = no symptom; 10 = very severe symptoms. Values are given as means and SD (in parentheses). *P* values at inclusion were not significant.

[†]Significantly different (lower) than controls $P < .05$; $P < .01$.

^{*}Significantly different (lower) in comparison with local treatment only ($P < .05$).

**FIG. 1.** Variations in ulcer size in the different treatment groups.

alterations, signs of allergic reaction, and any other manifestation.

The study was not sponsored by companies producing the materials and products quoted in the article. The compound was supplied, without conditions, by Horphag Research Management SA, Geneva, Switzerland.

RESULTS

All 30 included subjects completed the study. The age and male-female ratios were comparable among the different groups (Table 1). The reduction in ulcerated area and in symptomatic score was more evident and statistically significant ($P < .05$) in patients who had systemic plus local treatment (Table 2, Fig. 1). Oral treatment only and

local treatment alone were both less effective but significantly superior ($P < .05$) than the values in controls receiving just foot care.

The improvement in the microcirculation after treatment with Pycnogenol (Table 3) is demonstrated by an improvement (increase) in Po_2 and by a decrease (which is considered an improvement) in Pco_2 . Also, after treatment there was a lower flux at rest and a significantly higher level of venoarteriolar response, which are all considered an improvement in the microcirculation. All these parameters were significantly better than control values ($P < .05$).

As observed for the evaluation of ulcer healing, the best values demonstrating microcirculation improvement were obtained with the combined treatment. Treatments with Pycnogenol were superior to controls, which also improved as a result of medications and foot and wound care during the 6 weeks of the follow-up period.

Basically, Pycnogenol treatment, with different intensity of actions, made ulcer healing faster as, on average, 86% of the ulcerations were completely healed within 6 weeks (Table 2) compared with 61% of ulcerations completely healed in controls (Table 2; $P < .05$). The best healing rate (89% of ulcers completely healed) was obtained with the combination oral and local treatment.

No significant local or systemic side effects were observed during the 6-week treatment period.

DISCUSSION

As skin flux is increased, Po_2 decreased and Pco_2 increased (the result of chronic increase in capillary pressure, transmitted at the end of the microcirculatory levels), the aims of any treatment in diabetic microangiopathy are to reverse these microcirculatory changes.

TABLE 3. Microcirculatory Parameters.

Week	Pycno (Oral+Local)	Phyco (Oral)	Controls
Po ₂			
1	47 (4)	46 (3)	48 (4.2)
6	58 (3)**	55 (4)*	48 (3) NS
Pco ₂			
1	33 (2)	32 (3)	32 (2.2)
6	27 (3)*	28.8 (2)*	29.8 (3.3) NS
Flux at rest			
1	3.6 (1)	3.5 (0.7)	3.8 (0.2)
6	2 (0.7)*	2.1 (1)*	3.3.8 (0.8) NS
Venoarteriolar response			
1	8 (0-20)*	9 (0-21)*	9 (0-19)
6	22 (5-38)**†	12 (4-32)*	8 (3-23) NS

Flux at rest is expressed in LDF flux units. The venoarteriolar response is expressed in median and range. Po₂ and Pco₂ are in mmHg. P for all data at inclusion was not significant. Differences from inclusion values: *P < .05; **P < .01; †Difference (P < .05) with the other groups.

Elastic compression in patients with diabetic microangiopathy is effective in arresting the progression of neuropathy and microangiopathy, mainly by controlling edema.²¹ Elastic compression does not treat diabetic microangiopathy but is very effective in controlling edema during the daily hours of working and standing. Elastic stockings in clinical practice in diabetic microangiopathy decrease blood micropooling in the microcirculation, preventing edema and eventually improving skin perfusion,²⁰⁻²¹ and protect the skin from microtraumas, usually the starting event of ulcerations. The unbalanced nutritional status because of impaired microcirculation makes skin very delicate and unable to cope with the microtraumas that usually occur in normal daily activity. Diabetic ulcers, particularly those in the plantar weight-bearing region, are very difficult and slow to heal and tend to recur, causing high management costs.^{20,21}

Stockings, however, may be difficult to wear in hot climates/seasons, patients with ulcers may find it difficult to put them on, and stockings may also be contraindicated in limbs with reduced arterial perfusion. A different approach, the use of a pharmacologic agent such as Pycnogenol, may have a wider and safer range of applications in controlling ulcers. In this pilot study, oral Pycnogenol improved microcirculatory parameters and, consequently, ulcer healing, as indicated by the reduction in ulcer area and symptoms compared with the control group.

Several mechanisms may contribute to faster ulcer healing in diabetic microangiopathy. An improved glucose metabolism may be obtained with the glucose-lowering effect of Pycnogenol,^{22,23}

which may improve antidiabetic treatment. The anti-inflammatory effects, such as inhibition of nuclear factor- κ B,^{29,30} inhibition of adhesion factors,^{29,30,31} inhibition of cyclooxygenase,³² and inhibition of matrix metalloproteinases,³³ may reduce tissue inflammation. The important, antiedema effect of Pycnogenol acts by decreasing the pathologically high permeability of capillaries,³⁴ leading to edema reduction in high-perfusion microangiopathy.

The higher efficacy of the combined local and systemic treatment is probably associated with the higher local concentration of Pycnogenol in the ulcer area. Additionally, the astringent properties and bacteriostatic action³⁵ of Pycnogenol force and make faster the healing process.

CONCLUSION

These findings confirm the results of our previous study showing a faster healing of venous ulcers, comparable with diabetic ulcers, by treatment with Pycnogenol.³⁶ Because treatment with Pycnogenol offers a safe alternative to existing therapy, the combined oral and topical application of Pycnogenol should be subject to larger, controlled studies.

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