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Aescin-based topical formulation to prevent foot wounds and ulcerations in diabetic microangiopathy

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Abstract. – OBJECTIVE: Impairment of the peripheral microcirculation in diabetic patients often leads to severe complications in the lower extremities, such as foot infections and ulcerations. In this study, a novel aescin-based formulation has been evaluated as a potential approach to prevent skin breaks and ulcerations by improving the peripheral microcirculation and skin hydration.

PATIENTS AND METHODS: In this registry study, 63 patients with moderate diabetic microangiopathy were recruited. Informed participants freely decided to follow either a standard management (SM) to prevent diabetic foot diseases (n = 31) or SM associated with topical application of the aescin-based cream (n = 32). Peripheral microcirculatory parameters such as resting skin flux, venoarteriolar response and transcutaneous gas tension were evaluated at inclusion and after 8 weeks. In addition, several skin parameters of the foot area, such as integrity (as number of skin breaks/patients), hydration and content of dead cells were assessed at the defined observational study periods.

RESULTS: Improvements in cutaneous peripheral microcirculation parameters were observed at 8 weeks in both groups; however, a remarkable and significant beneficial effect resulted to be exerted by the aescin-based cream treatment. In fact, the microcirculatory parameters evaluated significantly improved in the standard management + aescin-based cream group, compared with baseline and with the standard management group. Similar findings were reported for skin parameters of the foot area.

CONCLUSIONS: The topical formulation containing aescin could represent a valid approach to manage skin wounds and prevent skin ulcerations in patients affected by moderate diabetic microangiopathy.

Key Words:
Diabetic microangiopathy, Microcirculation, Foot ulceration, Aescin.

Introduction

Diabetes mellitus is a metabolic disorder characterized by defective or deficient insulin secretory process, glucose underutilization and increased blood sugar. Hyperglycemia is responsible for a wide number of complications, among which vascular diseases are the most serious, representing the leading cause of morbidity and mortality in these patients[1-4].

In particular, hyperglycemia induces vascular damages probably through a single common pathway – increased intracellular oxidative stress – linking four major mechanisms: the polyol pathway, advanced glycation end-products (AGEs) formation, the protein kinase C (PKC)-diacylglycerol (DAG) and the hexosamine pathways[5]. Vascular diabetic abnormalities associated with diabetes include physiological and structural changes in microvessels (increased capillary thickness, increased vascular permeability, impaired autoregulation of blood flow and vascular tone) of the retina, kidneys, skin and peripheral nervous systems, leading to the development of the diabetic microangiopathy[6].

Impairment of the peripheral microcirculation in diabetes is often underdiagnosed until secondary complications in the lower extremity, such as foot infections and ulcerations, become evident[7]. The prevalence of foot ulcerations is estimated to range from 4% to 10%, whereas the lifetime risk for the development of a diabetic foot ulcer in patients with diabetes ranges from 15% to 25%[8]. However, giving the increased prevalence of diabetes predisposing factors, the burden of diabetic foot ulcer is expected to raise in the future. Consequently, the social and economic burden of diabetic foot infections and ul-

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cerations is substantial: as a matter of example the cost of diabetic foot care in 2010-2011 was estimated at UK£580 million, the 0.6% of the National Health Service expenditure in England in that period of time[9].

Synergic treatments and preventive actions are crucial to avoid the consequences of the diabetic microangiopathy. To this end, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine developed clinical practice guidelines including several preventive recommendations such as adequate glycemic control, periodic foot inspection, patient and family education[10,11].

Topical remedies based on naturally-derived active agents could also represent an effective alternative strategy to prevent these ulcers by improving peripheral microcirculation.

Aescin, the major active component found in horse chestnut (*Aesculus hippocastanum L.*) seed extract, presented at least three pharmacodynamic actions: anti-edematous properties, anti-inflammatory activities and venotonic properties[12-14]. In particular, aescin-based treatments have already shown beneficial effects in chronic venous insufficiency and associated ulceration, hemorrhoids and post-operative oedema[15-20].

In order to prevent foot ulcerations in diabetic patients with diabetic microangiopathy, in this registry study, we evaluated the efficacy and safety of a topical formulation containing aescin. In particular, we investigated the effect of the topical product on peripheral skin microcirculation and foot skin hydration.

Patients and Methods

This was a registry study conducted in 63 patients suffering from diabetic microangiopathy, with a high risk of developing foot ulceration. Diabetes (glycated hemoglobin > 7.5%) was diagnosed at least 5 years before the study period and patients were treated with oral antidiabetic agents and diet. Color duplex scanning was performed to exclude recently (< 1 year) arterial/venous obstruction or thrombosis and to define the presence of peripheral vascular disease. Doppler ultrasound test was carried out to evaluate tibial pulses (detectable, with at least 2 phases, in all feet examined) in order to exclude patients with severe ischemia and necrosis associated to peripheral arterial disease. Only patients with moderate microangiopathy were included.

All participants gave written informed consent before enrollment. All procedures received local Ethics Committee approval, in accordance with the latest version of the Declaration of Helsinki. Informed participants (n = 63) freely decided to be enrolled in the following groups: the standard management (SM) only (n = 31); SM associated with topical application of an aescin-based cream (n = 32). Standard management (SM) of diabetic microangiopathy associated with high risk of foot ulceration included: adequate glycemic control, use of neutral washing agents, antifungal drugs, friction-free socks and soft shoes. Treatment with aescin-based cream consisted of 3 g specific formulation application on the foot skin twice a day, after detersion (30 min in water at 40°C with neutral soap).

Each individual was subjected to blood tests and non-invasive clinical and instrumental examinations at the following time period: at inclusion and after 8 weeks. The following tests were performed:

- Laser Doppler Flowmetry (LDF): resting skin flux and venoarteriolar response measurements were performed by Vasoflo (Vasamedics, St. Paul, MN, USA), as described previously[21]. Briefly, two measurements were taken on the dorsal and plantar surface of the foot, on intact skin, at constant room temperature (21°C).
- Transcutaneous oxygen and carbon dioxide tensions ($tcPO_2$ and $tcPCO_2$): quantitative evaluations of the cutaneous gas exchange were assessed by Microgas Combisensor (Kontron Ltd, Chichester, UK), as described previously[21].
- Foot inspection to evaluate and measure skin breaks
- Bio-Impedance Analysis (BIA): the content of water in the skin and the quantity of dead skin cells were assessed by EP-HYDR8 (Irvine, CA, USA). The evaluation was expressed by an arbitrary scale ranging from 0 (very hydrated) to 5 (very dehydrated) for water content; from 0 (soft skin) to 5 (exfoliating skin) for dead skin cells.

Statistical Analysis

Comparisons of numerical data were performed by the non-parametric test, Mann-Whitney U-Test. A p-value < 0.05 was considered statistically significant.

Table I. Details of the patients enrolled in the study.

	Standard management	Standard management + aescin-based cream
Subjects (female)	32 (13)	31 (11)
Age, years (mean ± SD)	51.1 ± 4.4	52.2 ± 3

SD: standard deviation.

Results

Details of the study groups are shown in Table I. The two groups presented similar demographics (Table I) and clinical characteristics (Table II) at inclusion. In particular, as diabetic microangiopathy patients, resting skin flux, transcutaneous gas tensions and venoarteriolar response were altered respect to normal subjects, in both groups at inclusion. Overall, improvements in cutaneous peripheral microcirculation parameters were observed at 8 weeks in both groups. However, a remarkable and significant beneficial effect resulted to be exerted by the aescin-based cream treatment. In fact, the initially abnormal resting skin flux (2.4 ± 0.3) significantly decreased upon treatment with the formulation containing aescin, at 8 weeks (1.9 ± 0.4) (Figure 1 Table II). Similarly, the other microcirculatory parameters evaluated significantly improved in the standard management + aescin-based cream group, compared to baseline (Table II). Moreover, the treatment with the aescin-based formulation resulted more effective than the only standard management in ameliorating all the cutaneous microcirculation parameters (Table II). Table II and Figure 2 summarizes also the assessment of several skin parameters of foot area, such as integrity (as number of skin breaks/patients), hydration and content of dead cells. Consistent with the previous data, Globally favorable were also the results of this skin parameters in the group treated with the cream containing aescin (Table II).

The topical formulations containing aescin was very well tolerated by all subjects. Neither clinically relevant variations in the blood parameters, nor local problems were observed over the study period.

Discussion

Diabetic foot problems are associated with considerable morbidity and mortality. In fact, in addition to a dramatic deterioration of the quality of life, patients with diabetic wounds and amputations seem to have worse outcomes than patients with some forms of cancer[22]. Peripheral skin microcirculation plays a prominent role in maintaining skin integrity; disturbances in the microcirculatory functions together with neuro-

Table II. Microcirculatory and skin parameters in standard management group and standard management + aescin-based cream group.

	Standard management		Standard management + aescin-based cream	
	Inclusion	8 weeks	Inclusion	8 weeks
Microcirculatory parameters				
VAR	22.4%	23%	22.4%	31%*†
$tcPO_2$ (in mmHg)	48.3 ± 1.9	48.4 ± 2	48.1 ± 3	50 ± 1.6*†
$tcPCO_2$ (in mmHg)	27.6 ± 1	28.1 ± 1.1	27.4 ± 1.2	29.2 ± 1.1*†
Skin parameters				
Skin breaks < 1 mm (number/patient)	6.5 ± 0.5	5.3 ± 1.1	6.6 ± 1	2.5 ± 1.2*†
Skin breaks > 2 mm (number/patient)	0.5 ± 0.5	0.4 ± 0.3	0.6 ± 0.3	0.2 ± 0.1*†
Skin dryness (range 0-5)	3.3 ± 0.4	3.3 ± 1	3.4 ± 0.8	1.7 ± 1.1*†

Data are expressed as mean ± standard deviation. *$p < 0.05$ *vs*. inclusion; †$p < 0.05$ vs. standard management group.

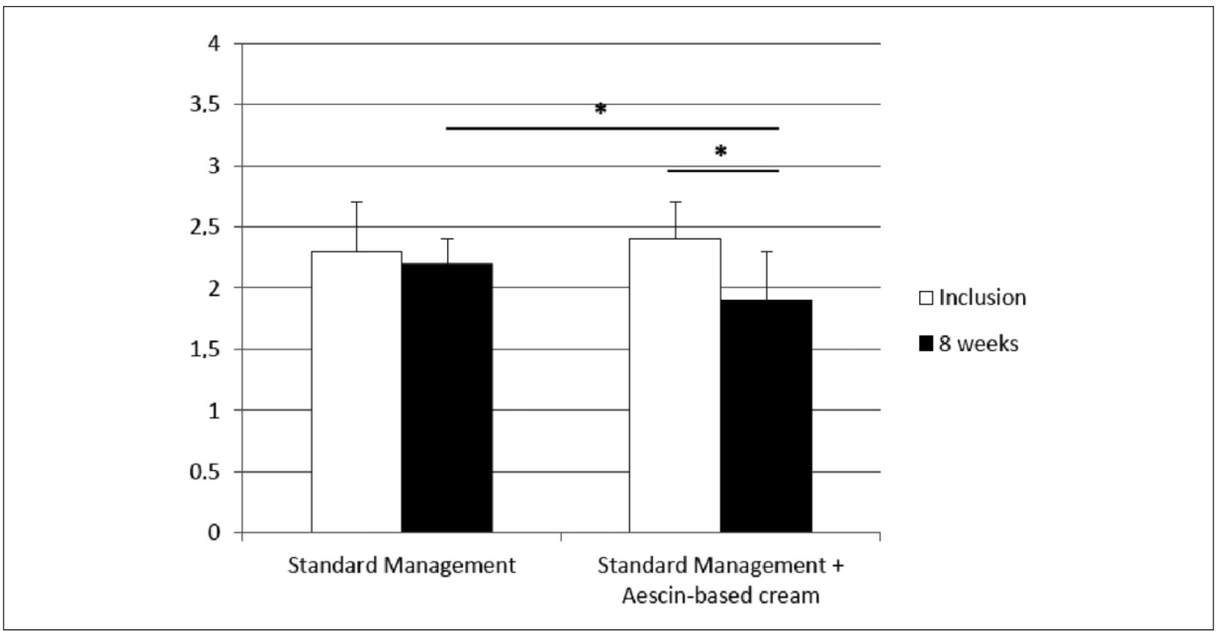

Figure 1. Evaluation of the resting skin flux by Laser Doppler Flowmetry. Data are shown as mean±standard deviation. *$p < 0.05$.

logic and vascular complications contribute to diabetic foot ulcerations and poor healing of wounds[23].

The management of diabetic microangiopathy with a high risk of foot ulceration includes the control and prevention of the risk factors; the measurements of microcirculatory parameters could be clinically used to monitor the evolution of diabetic foot diseases and the effects of potential therapies.

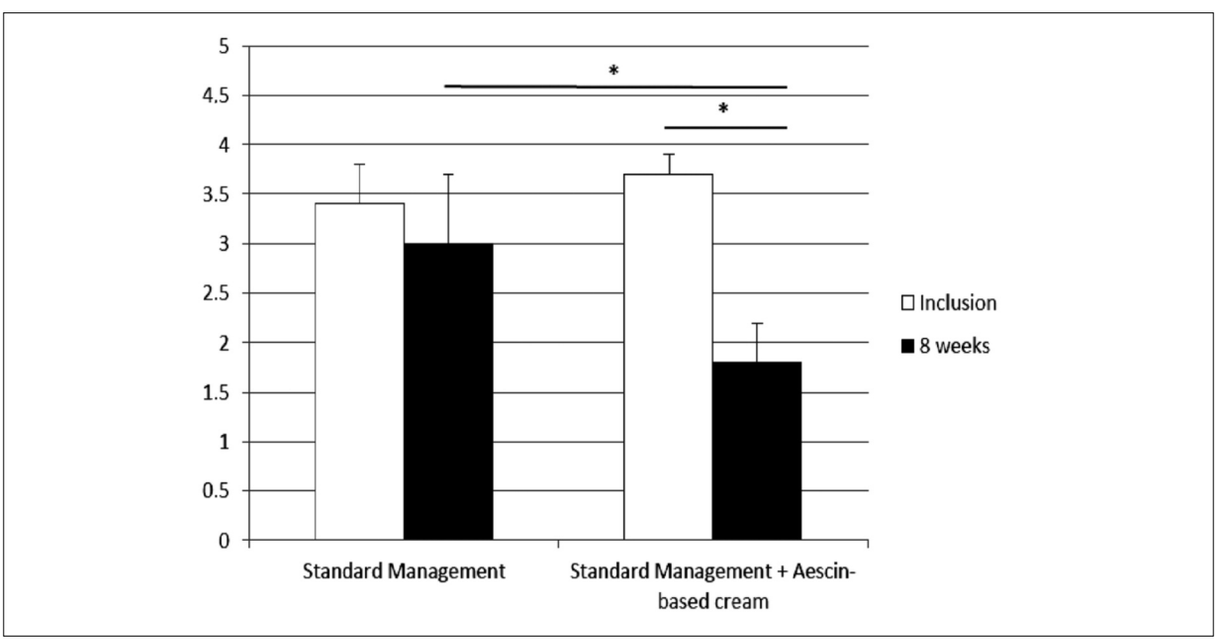

Figure 2. Evaluation of the content of dead cells on foot skin by EP-HYDR8. Data are shown as mean ± standard deviation. *$p < 0.05$.

For instance, increased skin blood flow and impaired venoarteriolar response cause oedema and may contribute to the thickening of capillary basement membranes and to the progression of diabetic microangiopathy[24]. Moreover, on the other hand, adequate tissue oxygenation is an essential factor for wound healing: the constant presence of oxygen in tissues limits bacterial growth following skin breaks, allows a functional white cells distribution leading to a more controlled inflammatory response. In this study, a novel aescin-based formulation has been developed as a natural and tolerable approach to prevent skin breaks and ulcerations by improving the peripheral microcirculation and skin hydration. Although all the limitations of any registry study should be taken into account, the aescin-based cream showed beneficial effects in all the skin microcirculatory parameters such as resting skin flux, venoarteriolar response and transcutaneous gas tension, evaluated at inclusion and at 8 weeks. These microcirculatory improvements, together with an increased skin hydration, made the foot skin less prone to breaking.

Conclusions

In diabetic microangiopathy, local treatment with a cream containing aescin improved the peripheral microcirculation and skin hydration, leading to a reduced number of skin breaks. Therefore, this product containing aescin could represent a valid approach to manage skin wounds and prevent skin ulcerations in patients affected by moderate diabetic microangiopathy.

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Conflict of Interest

ST and GM are employees of Indena S.p.A. LG is a consultant for Indena S.p.A. The other Authors declare no conflicts of interest.

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