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Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study

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Aim. The aim of the present study was to evaluate the improvement of diabetic microangiopathy in patients suffering from this condition since at least five years, and whose disease was managed without insulin.

Methods. Curcumin, the orange pigment of turmeric, has recently received increasing attention because of its antioxidant properties, mediated by both direct oxygen radical quenching and by induction of anti-oxidant responses via Nrf2 activation. This aspect, combined with the beneficial effects on endothelial function and on tissue and plasma inflammatory status, makes curcumin potentially useful for the management of diabetic microangiopathy. To further evaluate this, Meriva, a lecithinized formulation of curcumin, was administered at the dosage of two tablets/day (1 g Meriva/day) to 25 diabetic patients for four weeks. A comparable group of subjects followed the best possible management for this type of patients.

Results. All subjects in the treatment and control group completed the follow-up period; there were no dropouts. In the treatment group, at four weeks, microcirculatory and clinical evaluations indicated a decrease in skin flux ($P < 0.05$) at the surface of the foot, a finding diagnostic of an improvement in microangiopathy, the flux being generally increased in patients affected by diabetic microangiopathy. Also, a significant decrease in the edema score ($P < 0.05$) and a corresponding improvement in the venoarteriolar response ($P < 0.05$) were observed. The PO_2 increased at four weeks ($P < 0.05$), as expected from a better oxygen diffusion into the skin due to the decreased edema. These findings were present in all subjects using Meriva, while no clinical or microcirculatory effects were observed in the control group.

Conclusion. Meriva was, in general, well tolerated, and these preliminary findings suggest the usefulness of this curcumin formulation for the management of diabetic microangiopathy, opening a window of opportunities to be evaluated in more prolonged and larger studies. The molecular mecha-

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nisms involved in the beneficial effects of curcumin on microcirculation and edema are also worth investigation.

KEY WORDS: Curcumin - Diabetic angiopathies - Diabetes mellitus - Microcirculation - Laser Doppler flowmetry - Edema.

Diabetic patients, especially those with suboptimal glycemic control, are at risk for oxidative stress and its associated complications, and have therefore an increased requirement for anti-oxidant factors.¹ Endothelial cells are a primary site of oxidative damage, and much research has been devoted to the role of anti-oxidants and vitamins in the prevention of diabetic complications secondary to endothelial damage. Interesting and promising results have been observed in cellular systems and animal models of the disease,¹ and the concept of "anti-oxidant shield" for the prevention, or the attenuation, of diabetes-associated symptoms has received an important clinical validation with bardoxolone methyl, an antioxidant inflammation modulator (AIM) that is currently undergoing phase 3 study for the treatment of diabetic kidney disease.²⁻⁴

Diet is a major source of anti-oxidant agents, and there is no shortage of potential dietary ingredients that could, in principle, play a positive role for the

This project is part of the diabetic Cloud study

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prevention, or the limitation, of the ravaging vascular effects of diabetes. Pycnogenol, a mixture of procyanidins from pine bark, has showed a promising clinical activity,⁵ while preliminary data suggest that curcumin, the orange pigment of turmeric, could improve endothelial function and oxidative stress in diabetic patients.⁶ Curcumin shows antioxidant properties mediated by both direct oxygen radical quenching and by induction of anti-oxidant responses *via* Nrf2 activation,⁷ and potently inhibits a host of factors involved in inflammation.⁷ Given the role of inflammation and oxidative stress in the development of diabetes complications,¹ it is not surprising that curcumin has shown a promising activity in several preclinical models of diabetic nephropathy,⁸ neuropathy,⁹ retinopathy,¹⁰ and encephalopathy.¹¹ Taken together, the results of these studies suggest that adjuvant therapy with curcumin might have an important beneficial role in attenuating diabetes-associated symptoms,¹² while the activity of curcumin on chloride currents in pancreatic β -cells even suggests a direct anti-diabetic activity.¹³

The improvement of diabetes-induced endothelial dysfunction has been extensively investigated at the clinical level, and represents one of the main targets of an ongoing project (Cloud) aimed at the prevention of diabetes complications. Several studies from our group have evaluated diabetic microangiopathy and the effects of different compounds on microangiopathy and its complications,¹⁴⁻²⁴ setting the standards for the evaluation of this condition in diabetics and the effect of management measures adopted to address it. While there was a strong rationale for extending these studies to curcumin, we were, nevertheless, aware that this compound shows a very poor oral bioavailability, responsible for the dramatic gap between the profligacy of its pre-clinical profile and the dismal poverty of its clinical documentation of activity.¹² To overcome the bioavailability issue, we have therefore focused on Meriva, a lecithin-formulation of curcumin developed by taking inspiration from the dietary association of turmeric to fatty dishes and the promising results obtained with the improvement of bioavailability associated to the lecithin-formulation (phytosome) of other poorly bioavailable phenolics.²⁵ An improved bioavailability (around 30 fold) has been demonstrated for Meriva compared to unformulated curcumin,²⁵ and its efficacy was successfully evalu-

ated in a series of clinical studies on inflammatory conditions.²⁶⁻²⁸

We present here an evaluation on the improvement of diabetic microangiopathy associated to the administration of Meriva, focusing on patients suffering for this condition for at least five years, and whose disease, managed without insulin, was characterized by microcirculatory alterations.

Materials and methods

All subjects at inclusion were showing microcirculatory alterations previously described and defined in several publications:²⁹⁻³⁶ 1) laser Doppler flowmetry (LDF)³⁵⁻⁴⁰ indicated: a) increased skin flux at the foot; b) decreased venoarteriolar response; 2) transcutaneous PO₂: indicated a decreased transcutaneous PO₂ (at the dorsum of the foot);⁴¹⁻⁴⁵ 3) evaluation of edema: edema/swelling at the foot (the hallmark of diabetic microangiopathy) was evident, particularly in the evening, disappearing after night rest. It was present in all patients (both limbs) at inclusion.

LDF measurements were obtained, as previously reported³⁰⁻³⁸ in a room at constant temperature (21-22° C) after 30 minutes of acclimatization and resting supine. The resting flux (RF) was measured at the dorsum of the foot (average of one minute of measurement; Vasamedics, Flowmeter, St Paul, MN, USA). The patients were asked to stand and the flux on standing was measured. The decrease in skin flux on standing is generally in the order of 40-50% of the RF in normal subjects. In diabetics the venoarteriolar response (VAR) is usually decreased as an alteration of the axon reflex defining the perfusional value on standing. This protective mechanism, controlling the amount of open capillaries when standing, is at the basis of the formation and control of edema. In diabetics with neuropathy and microangiopathy the VAR is reduced and edema, the hallmark of diabetic microangiopathy, is increased as a failure in constricting the capillary bed for absence or reduction of a sensing mechanism affected by the concomitant neuropathy. Transcutaneous PO₂ was measured at the dorsum of the foot with a CombiSensor and a Kontron (UK) PO₂ transcutaneous analyzer.

Edema was measured with the simplified clinical edema scale shown in Table I. Also the Karnofsky scale of these patients was recorded (Table II).

TABLE I.—*Edema definition and scoring.*

Score	Characterization	Localization
1.	No edema	
2.	Mild edema, visible only in the evening, one or both limbs	Distal: foot, ankle
3.	Moderate edema, disappears with night rest	Legs, below knee
4.	Generalized edema (hands included)	Above knee, diffuse
Does not disappear with night rest		

TABLE II.—*The Karnofsky Scale.*⁴⁶

100	Normal no complaints; no evidence of disease. Able to work.
90	Able to carry on normal activity; minor symptoms. Able to work.
80	Normal activity with effort; some symptoms. Able to work.
70	Cares for self; unable to carry on normal activity. Independent; not able to work.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing.

Included patients

Patients were characterized by no other clinical or metabolic disorder or important cardiovascular risk factor (excluding diabetes). The duration of the diabetes — from the first signs/symptom. — was on average 5.33;1.9 years (including both the supplement and the control groups, with no significant differences among groups). Main patients characteristics are summarized in Table III.

Peripheral vascular disease

No significant atherosclerotic disease was clinically present in the patients. Also no decrease in peripheral pressure or flow (measured by Doppler ultrasound at the femoral, popliteal and tibial arteries) had been observed before inclusion.

Treatment

Meriva at the dosages of two tablets/day (1 g Meriva/day) was administered for 4 weeks. In this study, a finished form prepared by Sigmar SpA (Almè, Berga-

TABLE III.—*Details of diabetic patients (no history of diabetic ulcerations; no other drugs needed for management; no previous use of insulin).*

	Curcumin patients	Controls
Number	25	25
Age	58.1;3.5 years	56.4;4.3
Range	50-65	50-65
Males	14	15

mo, Italy) was used. No insulin had been used before or was used during the observation period. All patients were managed with what could be considered the best management protocol for their type of pathology. The Meriva group simply added the product, as a supplement to the standard management that had been stable for at least 3 months before the inclusion in the study.

Basic treatment

All patients used oral antidiabetic agents and followed the appropriate diet. The BMI at inclusion was on average 24.5;1.3 and did not change during the observation period.

Statistical analysis

All measured target parameters have a non-normal, skewed or unknown distribution. Therefore the ANOVA (with the Bonferroni correction) was used to evaluate before-after results and the Mann-Whitney U-test to evaluate statistically significant differences (i.e. edema, Karnofsky scale).

A numerosity of at least 20 comparable, stratified microangiopathy patients per group (treatment versus control) was considered necessary to overcome the possible, unavoidable even under the best experimental conditions, differences due to the variability of the microcirculatory target measurements or parameters, particularly ultrasound LDF and PO₂ tests.

TABLE IV.—Microcirculatory measurements (VAR = venoarteriolar response), edema and the Karnofsky scale.

	Inclusion	4 weeks	P
1. LDF flux			
Curcum	3.32;0.8 flux units	2.35;0.72	<0.022
Controls	3.33;0.7	3.2;1	ns
2. VAR			
Curcum	23.4% (12-39.5)	39.7 (15-44.4)	<0.05
Controls	24.1(13-44.4)	24.6 (12-42)	ns
3. Tc-PO2			
Curcum	42.6;7.4 mmHg	49.3;4.4	<0.02
Controls	43.1;4.3	42.3;4.4	ns
4. EDEMA (0-3)			
Curcum	2.22;1.2	1.53;1.33	<0.025
Controls	2.23;0.7	2.2;0.8	ns
KARNOFSKY *			
Curcum	84.2;8.8	89.6;4.8	<0.05
Controls	85.8;7.2	83.5;3.7	ns

*Karnofsky Scale:

100 Normal; no complaints; no evidence of disease. Able to work.

90 Able to carry on normal activity; minor symptoms. Able to work.

80 Normal activity with effort; some symptoms. Able to work.

70 Cares for self; unable to carry on normal activity. Independent; not able to work.

Results

All subjects (treatment and controls) completed the study, lasting between 28 and 35 days with an average of 28.83;2.1 days; there were no drop-outs.

At 4 weeks, microcirculatory and clinical evaluations (Table IV) indicated:

— a progressive decrease in skin resting flux ($P<0.05$) at the surface of the foot. This observation indicates an improvement in the level of microangiopathy as skin flux is generally increased in diabetics with microangiopathy;

— a significant decrease in the edema score ($P<0.05$) and a significant improvement in the venoarteriolar response ($P<0.05$). The presence of edema is associated with the failure in venoarteriolar response, therefore the two measurements are closely linked;

— an increase of PO_2 at four weeks with a significant improvement, possibly associated to the decrease in skin edema allowing a better PO_2 exchange and diffusion into the skin ($P<0.05$). This may result in a decreased incidence in skin lesions in time. However this was not evaluated in this study (the study would need a larger number of patients and a much longer follow-up).

It is important to observe that these observations were present in all subjects using curcumin. Considering these target measurements, there were no clinically visible effects in controls.

The Karnofski scale was also improved ($P<0.05$) in the Meriva group in comparison with controls (Table IV).

Tolerability

The treatment (supplementation) was well tolerated in all subjects and most patients decided to continue with curcumin after the study period.

The Therapeutic Proposal Registry

In this new type of study – specifically defined for food supplements rather than for defined drug treatment. — a series of therapeutic/management proposals are made to the observed patients. It is completely up to them to choose to follow the proposed management systems. Even the follow up period is not defined and may be variable (within a range of days/weeks needed to complete the observation). The supplement, generally, is not supplied and the patients use their means to purchase the product or pursue the proposed management system/plan.

Actually the patients' willingness to follow the protocol is one of the positive points in evaluation, as patients tend to follow instructions when they observe or feel benefits. Also when it is convenient for them (even from a cost point of view) to solve their problems, patients tend to use what they consider useful for their specific condition.

Discussion

The presence and evolution of diabetic microangiopathy can now be evaluated in a qualitative and quantitative way²⁹⁻⁴⁵ in its different, complex, and interactive aspects. Thus, by using laser-Doppler flowmetry in association with other noninvasive microcirculatory techniques (*i.e.*, transcutaneous PO_2 and PCO_2 and capillary filtration measurements) two major types of peripheral microangiopathies can be recognized:

1. a low perfusion microangiopathy (LPM) generally associated to ischemia, observed in peripheral vascular disease, essential hypertension, Raynaud's disease (in association with vasospastic conditions);

2. a high perfusion microangiopathy (HPM) observed in venous hypertensive microangiopathy and diabetic microangiopathy. In both these conditions there is an increased skin flux, decreased venoarteriolar response and increased capillary filtration leading to chronic edema formation.

In HPM, elastic compression and drugs acting on edema and capillary filtration effectively reduce skin flux, the capillary leakage and the edema formation. Diabetic microangiopathy is the most frequent conditions of HPM, causes a large number of important complications, often leading to ulcerations and feet amputations.⁴⁰⁻⁴⁴

Several studies from our group have evaluated diabetic microangiopathy and the effects of different compound and physical management methods (elastic compression, exercise) on this microangiopathy and on its most common complications. These studies have defined some microcirculatory evaluation standards for the quantitative evaluation of diabetic microangiopathy. Therefore changes produced by management measures or treatment can be quantitatively and prospectively measured. The methods of evaluation and quantification of microangiopathy in the present study require standardized environmental conditions to avoid excess of variability of the target measurements. All measurements were made before 10 a.m. in the morning avoiding any stimulant food or drink and after resting and acclimatization.

The extent of a concomitant arterial atherosclerotic damage can be quantified with other noninvasive screening methods based on ultrasound. The increase in capillary filtration (consequence of a massive vasodilatation of the capillary system) is associated with a significant decrease of venoarteriolar response in almost all diabetics.^{42, 43} To quantify capillary filtration venous occlusion plethysmography and the rate of ankle swelling (strain gauge plethysmography) can be used to quantify the filtration into the extracapillary compartment. These methods indicate the mechanism of the formation of peripheral edema, the most frequent sign, the hallmark, in diabetic microangiopathy. Other methods (i.e. the vacuum suction chamber and the edema tester) can be used to assess changes due to treatments or management changes in diabetic microangiopathy but require time and are moderately costly. Also the changes in renal damage^{46, 47} can be assessed in these patients i.e., by measuring proteinuria. The alterations in carotid-femoral arterial walls⁴⁸ and retinal perfusion⁴⁹

and flow characteristic may be effective to quantify and follow in time patients with retinal microangiopathy. Therefore a number of target organs may be noninvasively evaluated to define the clinical value of micro and macroangiopathy in diabetics.

Using this strategy, we have demonstrated that curcumin as Meriva has a potential role in the management of diabetic microangiopathy, opening a new window of opportunity worth evaluating in more prolonged and larger studies. It is also interesting to remark that fibrinolytic enhancement was observed in some patients, particularly those with a mild increase in fibrinogen levels and altered fibrinolysis. Finally, the results of this study will, hopefully, foster further clinical studies on the role of dietary ingredients for the attenuation of the damaging effects of the vast arrays of pathologies whose molecular hallmark is the presence of a "silent" inflammatory status.¹²

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