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Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy

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Background. **In the present study, the improvement of diabetic microangiopathy and retinopathy was evaluated in 38 diabetic patients treated with a novel curcumin phospholipids delivery form (Meriva®).**
Methods. **Diabetes was diagnosed at least 5 years before inclusion and all patients had signs of retinal oedema and of peripheral microangiopathy. Meriva® was administered at the dosage of 2 tablets/day (each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) for a period of at least 4 weeks in addition to the standard management plan, while a comparable group of subjects (n = 39) followed the standard management plan alone.**
Results. **All subjects (treatment and controls) completed the follow-up period, there were no dropouts and Meriva® showed an optimal tolerability. At 4 weeks, microcirculatory and clinical evaluations indicated an improvement of microangiopathy. In terms of peripheral microangiopathy, in the Meriva® group, there was a significant improvement in the venoarteriolar response ($p<0.05$) and a decrease in the score of peripheral oedema ($p<0.05$), a sign typically associated with the failure of the venoarteriolar response. At the retinal level, high-resolution, duplex scanning, used to measure retinal flow, showed improvements in the Meriva® treated patients. The evaluation of retinal oedema (Steigerwalt's scale) showed an improvement associated with improved visual acuity (Snellen scale). There were no clinical or microcirculatory effects in controls.**
Conclusions. **These preliminary observations, indicate the value of curcumin, when administered in a bioavailable form as with Meriva®, in the management of diabetic microangiopathy and retinopathy.**

KEY WORDS: Meriva® - Curcumin - Diabetic microangiopathy - Diabetes - Retinal microangiopathy - Microcirculation - Laser doppler - Oedema.

Microangiopathy refers to a vascular condition (angiopathy) affecting small vessels, as opposed to macroangiopathy, which on the contrary affects large vessels. One of the most frequent causes of its occurrence is the presence of long terms diabetes mellitus, responsible for chronic hyperglycaemia. Endothelial cells are exposed to high blood glucose levels, leading to glycation of surface proteins and accumulation of advanced glycation end products, which in turn initiate pro-inflammatory processes involving NF-κB activation and subsequent expression of endothelial cell adhesion molecules (with the resulting leukocyte adhesion).[1-3] Also, matrix metalloproteinases (MMPs) can play a decisive role in the remodelling of extracellular matrix and can be involved in causing changes to vascular permeability.[4] Therefore, the vascular walls become abnormally thick but weak, and vessels can bleed, leak proteins, with an overall reduced perfusion in the body. Typical expressions of this microangiopathy may be located in the kidney (diabetic nephropathy), in the nerves (diabetic neuropathy) or in the retina (diabetic retinopathy). Diabetic retinopathy is a major cause of blindness in people with diabetes and represents one of the most feared complications. According to the National Institute of Health 40%

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to 45% of American citizens diagnosed with diabetes already have some stage of diabetic retinopathy, which can progresses from non-proliferative or background retinopathy to proliferative retinopathy. Typical signs are represented by increased vascular permeability, tissue ischemia, and neovascularisation. Neovascularisation of the retina, in particular, can produce a high risk of blindness as a result of vitreous haemorrhage and fibrosis. An increasing attention is being devoted to the role of vascular endothelial growth factor (VEGF),[5] a potent angiogenic and vascular permeability factor, which can stimulate the formation of new vessels, enhance collateral vessel formation, and increase the permeability of the microvasculature in the retina with the disruption of the blood-retinal barrier. In patients with proliferative diabetic retinopathy VEGF levels have been found to be markedly elevated in the vitreous and aqueous fluids.[6] Similarly, a strong role of VEGF has been demonstrated in the onset of diabetic nephropathy, where VEGF is involved in the induction of hyperfiltration, albuminuria, and glomerular hypertrophy.[7] Finally, another important aspect to be considered in diabetic patients is the role of chronic oxidative stress featured in this condition: accumulating evidence indicates that ROS (reactive oxygen species) have an important role in the onset of diabetic complications, in particular vascular ones.[8] Many biochemical pathways strictly associated with hyperglycaemia (glucose autoxidation, polyol pathway, prostanoid synthesis, protein glycation) can induce an increase in the production of free radicals.[9] Furthermore, exposure of endothelial cells to high glucose concentrations leads to augmented production of superoxide anion, which may quench nitric oxide, a potent endothelium-derived vasodilator that participates in the general homeostasis of the vasculature. It is, hence, noteworthy the fact that many antioxidants are able to counteract and reverse the noxious effects of high glucose levels on the vascular system.[10-14]

Curcumin, the yellow dye of *Curcuma longa*, is endowed with a pleiotropic mechanism of action, which makes it potentially useful in diabetes management, as it associates anti-inflammatory, antioxidant and VEGF inhibition properties, to name a few.[15-18] Curcumin is endowed with a very low acute and chronic toxicity, but is poorly absorbed. To overcome the absorption barrier, megadoses have been used in some studies, failing, however, to provide concentrations of clinical relevance. On the other hand, it has been demonstrated that suitable formulation can overcome the inherently dismal oral absorption of curcumin. Given the role of inflammation and oxidative stress in the development of diabetes complications, it is not surprising that curcumin has shown a promising activity in several preclinical models of diabetic nephropathy, neuropathy, retinopathy, and encephalopathy. Taken together, the results of these studies suggest that adjuvant therapy with curcumin might have an important beneficial role in attenuating diabetes-associated symptoms, while the activity of curcumin on chloride currents in pancreatic β-cells even suggests a direct anti-diabetic activity.[19] Meriva®, a lecithin delivery system of curcumin, is endowed with superior bioavailability and tissue distribution compared to the unformulated natural product. In a previous study, Meriva® supplementation was already demonstrated able to improve diabetes induced endothelial dysfunction, an end-point that represents one of the main targets of an ongoing project (Cloud study) aimed at the prevention of diabetes complications. [20,21]

It was therefore interesting to further evaluate its potential in the realm of the management of diabetes complications, namely peripheral microangiopathy and diabetic retinopathy.

Subjects and methods

This pilot study focused, as the primary end point, on the improvement of diabetic microangiopathy in diabetic patients. Patients had a history of diabetes for at least 5 years, with a condition under adequate control at inclusion. These subjects were all managed without insulin and had diabetes characterized by microcirculatory alterations including retinopathy. Patients were characterized by no other clinical or metabolic disorder or important cardiovascular risk factor (excluding diabetes). The global BMI (Body Mass Index) at inclusion was on average 25.4;1.3 (range 24-26) and did not change during the observation period. The duration of diabetes – from the first signs/symptoms – was on average 5.61;1.1 years (considering both the Meriva® and the control group, with no significant differences between groups). Patients had no history of diabetic ulcerations, were not treated with other drugs nor reported previous use of insulin. No significant atherosclerotic disease was clinically present in these patients. Also no decrease

TABLE I.—*Oedema definition and scoring.*

Score	Characterization	Localization
0	No oedema	
1	Mild oedema, visible only in the evening	Distal, one or both limbs (foot, ankle)
2	Moderate oedema, disappears with night rest	Legs, below knees
3	Generalized oedema (hands included), doesn't disappear with night rest	Above knee, diffused

in peripheral pressure or flow (measured by Doppler ultrasound at the femoral, popliteal and tibial arteries) had been observed before inclusion.

Two management plans were compared:

— one including the current standard treatment (SM, which includes diet, exercise and oral antidiabetics)

— one including curcumin (administered as Meriva®) as a further complementary adjuvant factor in association with the SM.

All subjects at inclusion were characterized by microcirculatory alterations previously described and defined in several publications[22-25]:

1. Venoarteriolar response (VAR): Laser Doppler Flowmetry (LDF) was used to evaluate the VAR (decreased in all included subjects)

2. Oedema evaluation: oedema/swelling at the foot (the hallmark of diabetic microangiopathy) was evident, particularly in the evening, disappearing after night rest and was present in all patients (both limbs) at inclusion.

LDF measurements were obtained, as previously reported,[26-28] 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 1 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.[29,30] In diabetics the response (VAR) is usually decreased as an alteration of the axon reflex controlling the perfusion value while standing. The insufficiency of this protective mechanism, controlling the amount of open capillaries when standing, is at the basis of the formation of oedema. In diabetics, with neuropathy and microangiopathy, the VAR is reduced and oedema, 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.[31] Oedema (below the knee) was measured with the simplified clinical oedema scale shown in Table I.

TABLE IIA.—*Steigerwalt's classification to evaluate retinal oedema in stages.*

Stage (score)	Characterization
0	Normal retina
1	Fluid or exudate outside the macula in the posterior pole from 1 to 6 clock hours
2	Fluid or exudate outside the macula in the posterior pole from 6 to 12 clock hours
3	Fluid in the macula without cystic formations, with or with fluid or exudate in the rest of the posterior pole
4	Fluid in the macula with cystic formations (CME), with or with fluid or exudate in the rest of the posterior pole. The scores of the two eyes were averaged

TABLE IIB.—*Snellen scale (Visual acuity ranges).*

Score	Meaning
20/32 – 20/63	Mild vision loss
20/80 – 20/160	Moderate vision loss
20/200 – 20/400	Severe vision loss

At the retinal level, high-resolution, duplex scanning was used to measure retinal flow. A previously validated scale was used to evaluate the retinal oedema (Steigerwalt's scale[32] – Table IIA), while Snellen scale[33] (Table IIB) was used for visual acuity.

The study foresaw the supplementation of Meriva® for at least 4 weeks, with the microcirculatory and clinical evaluation at 4 weeks, and involved a total of 77 subjects. A group of 38 subjects (mean age 55.2;2.1 – 21 males, 17 females) completed the survey with at least 4 weeks of treatment with Meriva® in association with the SM. The SM alone (without Meriva®) was used in a control group of 39 volunteers of comparable age (mean age 54;3.2 – 22 males, 17 females) and severity of the condition.

Treatment: Meriva® tablets (manufactured by Indena S.p.A., each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) were administered at the dosage of 1 tablet twice/daily for at least 4 weeks shortly before meals. No insulin had been used before or was used during the observation pe-

TABLE III.—*Microcirculatory measurements (oedema, VAR), Snellen scale, retinal flow and retinal oedema results. At inclusion and after 4 weeks.*

ITEM	MERIVA® + SM		CONTROL (SM)	
Oedema score (0-3)	2.42;0.2	1.8;0.4#	2.4;0.3	2.3;0.2
VAR	25.3% (median) 18% – 34% (range)	38.4%* (median) 26% – 46% (range)	25.3% (median) 20% – 32% (range)	24.2% (median) 21% – 36% (range)
Snellen scale	20/122-20/155	20/32-20/78*	20/119-20/158	20/113-20/157
Retinal flow (peak systolic; cm/s)	26.4;2.2	28.9;2*	25.6;3.1	26.1;1.4
Retinal oedema	3.2;0.3	1.8;0.1*	3.11;0.2	3.1;0.2

*p<0.05 *vs.* inclusion; #p<0.025 *vs.* inclusion

riod. All patients were managed with what could be considered the best standard management protocol for this type of subjects (SM). The Meriva® group simply added the product, as a supplement to the their standard management that had been stable for at least 3 months before consideration of inclusion into the follow up.

Statistical analysis

All measured target parameters have a non-normal, skewed or unknown distribution. Therefore ANOVA (with the Bonferroni correction) was used to evaluate before-after results and the Mann-Whitney U-test for the evaluation of statistically significant differences (*i.e.* oedema). A numerosity of at least 20 comparable, stratified microangiopathy patients per group (treatment vs. control) was considered necessary to overcome the possible differences, unavoidable even under the best experimental conditions, due to the variability of the microcirculatory target measurements or parameters, in particular laser Doppler and ultrasound tests.

Results

All subjects (treatment and controls) completed the follow-up period, with no dropouts. The follow up and supplementation period lasted between 32 and 48 days with an average of 31.3;2.2 days. At 4 weeks, microcirculatory and clinical evaluations (as summarized in Table III) indicated:

a. a significant decrease in the oedema score in the Meriva® treated group vs. control (p<0.05)

b. a significant improvement in microcirculation in the Meriva® group, as shown by the changes in the median and range venoarteriolar response (VAR, p<0.05). The presence of oedema in diabetic patients with microangiopathy is generally associated to the failure in venoarteriolar response; therefore the two measurements (oedema and VAR) are closely linked.[34]

c. an improvement in visual acuity, as shown in the Snellen scale, in Meriva® patients in comparison with controls (p<0.025). The ranges of visual acuity were significantly improved in all Meriva® patients. There were minimal changes in visual acuity in controls in 4 weeks.

d. an improvemente of duplex scanning-measured retinal peak systolic flow velocity (measured by high-resolution color duplex, Preirus, Hitachi, Japan) in subjects using Meriva®. Also the diastolic components were (not significantly) increased in Meriva® patients.

e. an improvement in retinal oedema, associated with improved visual acuity in Meriva® patients in comparison with controls (p<0.05).

These positive, significant observations were consistently present in all subjects using Meriva®, while all target measurements were basically unchanged in controls. Blood pressure, heart rate and diabetic control (considering the dosages of the oral antidiabetic agents used) were unchanged in both groups.

Tolerability: the treatment (supplementation) was well tolerated in all subjects.

Discussion

This study (Cloud study) was structured as a "therapeutic proposal registry", similarly to previous ex-

periences conducted by our group.[21] In this new type of study – specifically defined for food supplements more than for defined drug treatments - a series of therapeutic/management proposal are made to the observed patients. It is completely up to them to follow the proposed management systems. Even the follow up period is not typically defined and may be variable (within a range of days/weeks) as needed to complete the observation. While this type of study is substantially different from those designed for drugs, it can nevertheless be more representative of real life conditions and of the way in which supplements are used when combined with standard treatment. Clinicians, generally, do not supply the supplement, and patients use their means to purchase the product or to 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 actually observe or feel benefits. Also when it is convenient for them (even from a costing point of view) to solve their problems patients tend to use what they consider useful for their specific condition.

An increasing evidence exists to document the usefulness of curcumin in diabetic and prediabetic conditions,[35,36] and its beneficial effects are difficult to be ascribed to a single mechanism of action: curcumin, in fact, confirms its pleiotropic behaviour in diabetes as well, where it exploits antioxidant effects, reduces the local activity of VEGF, directly promotes normal β-cells functionality, targets inflammatory status, reduces protein glycation and the subsequent build-up of tissue advanced glycation endproducts (AGEs) which contribute towards the pathogenesis of diabetic complications.[37-39] In particular, a subclinical or chronic inflammatory status has been recognized as being involved in the development of obesity, type 2 diabetes, and obesity-related atherosclerosis: while this mechanism of action is not sufficient to completely explain, alone, all the benefits produced by curcumin in these metabolic conditions, nevertheless it provides an interesting evidence to support the use of curcumin in association with standard medications and lifestyle changes.[40,41] According to the American Diabetes Association, in USA 25.8 million people – 8.3% of the population – are estimated to have diabetes. Out of these figures, 4.2 million people with diabetes aged 40 years or older had diabetic retinopathy in the period 2005 – 2008, with almost 0.7 million (4.4% of those with diabetes) affected by advanced diabetic retinopathy that could lead to severe vision loss. Dietary ingredients, able to counteract some of the causative factors involved in diabetes and its array of signs and symptoms, are definitely worth of consideration in order to try to reduce the burden of this disease and possibly delay the onset of its, often life threatening, complications.

Conclusions

This study, with these preliminary observations, indicates the potential value of curcumin (as Meriva®) in the management of diabetic microangiopathy, with a particular focus on peripheral microangiopathy and retinopathy. These preliminary findings, if confirmed by larger and more prolonged studies, may further extend the potential usefulness of Meriva® in diabetic complications, like diabetic neuropathy and nephropathy, as these latter conditions share several features common with the ones investigated, including the presence of a "silent" inflammatory status, the high level of ROS and the local increased activity of VEGF.

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Conflicts of interest.—S. Togni is Licensing Director of Indena, producer of Meriva. G. Appendino is consultant for Indena. The other authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. All the authors contributed equally to this work.