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High Dietary Fibre Intake (Talbina) as Adjunct in the Management of Diabetic Macular Edema

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To determine the efficacy of the lipid-lowering high dietary fibre (Talbina) in reducing retinal hard exudates and subfoveal lipid migration after focal/grid laser photocoagulation in clinically significant macular edema in patients with diabetes with elevated serum lipids. Thirty patients with type 2 diabetes with clinically significant macular edema, dyslipidemia and hard exudates of grade 4 and above were assessed in our study. Patient were subjected to strict metabolic control within 4 to 6 weeks of enrollment. In addition, 15 patients in group A received Talbina (Oats high dietary fibre); 15 patients in group B did not receive any lipid-lowering therapy. All received laser photocoagulation after a metabolic control period and were followed up for a minimum of 18 weeks. The outcome measures were reduction in hard exudates, subfoveal lipid migration, status of macular edema and visual acuity. The study included 19 men and 11 women with non insulin-dependent diabetes mellitus who could achieve good metabolic control within 4 to 6 weeks of inclusion in the study. All patients had elevated serum lipids at baseline. Ten (66.6%) of 15 patients in treatment group A and two (13.3%) of 15 patients in control group B showed reduction in hard exudates ($p = 0.007$). None of the patients in group A showed subfoveal lipid migration after laser photocoagulation, while five (33.3%) of 15 in group B showed subfoveal lipid migration ($p = 0.04$). Regression of macular edema was seen in nine eyes in group A and five in group B ($p = 0.027$). None of the eyes in group A showed worsening of visual acuity ($p = 0.22$). The use of high dietary fibre (Talbina) in patients with type 2 diabetes with dyslipidemia reduces the severity of hard exudates and subfoveal lipid migration in clinically significant macular edema and could be an important adjunct in the management of clinically significant macular edema.

Key words: Talbina (oat high dietary fibre), dyslipidemia, hard exudates

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INTRODUCTION

Patients with diabetes mellitus are known to have severe lipid abnormalities, namely hypercholesterolemia and elevated serum triglycerides (Doman *et al*., 1982; Larson *et al*., 1999; Biljana *et al*., 2004) The Wisconsin epidemiologic study of diabetic retinopathy in a cross-sectional study found that elevated serum cholesterol levels were associated with increased severity of hard exudates (Klein *et al*., 1991). This was further confirmed by Early Treatment Diabetic Retinopathy Study (Chew *et al*., 1996) (ETDRS), which demonstrated that elevated serum lipid levels were associated with an increased risk of retinal hard exudates. The observational data from ETDRS suggested that lipid-lowering drugs may decrease the risk of hard exudate formation and also preserve vision in patients with diabetic retinopathy. Studies performed during the 1960s, however, had found a corn oil-enriched diet (King *et al*., 1963) or atromid (Duncan *et al*., 1968) to be of limited use.

In a pilot study, Gordon *et al*. (1991) studied the effect of pravastatin, an inhibitor of 3-hydroxy-3-methy1-glutary1 coenzyme A (HMG-CoA) reductase in six patients with diabetes with non proliferative diabetic retinopathy and found the drug to be beneficial in improving the retinopathy and hard exudates. In a more recent study, another HMG-CoA reductase inhibitor, simvastatin, was found to retard the progression of retinopathy in patients with diabetes with hypercholesterolemia (Sen *et al*., 2002; Gupta *et al*., 2004) However, all of these drugs had toxic effect on the liver with highly elevated liver enzymes during the period of treatment.

MATERIALS AND METHODS

Thirty patients with non insulin-dependent diabetes mellitus with non proliferative diabetic retinopathy and macular edema characterized by the presence of retinal thickening within one disc diameter of the center of the macula that was associated with hard exudate grade 4 or more (ETDRS RG, 1991). The patients were included in the study if they had the following: (1) diabetes mellitus of at least 5 years duration; (2) abnormal baseline lipid profile (serum cholesterol ≥200 mg dL^{-1}, low density lipoprotein [LDL] ≥100 mg dL^{-1}, or serum triglycerides ≥200 mg dL^{-1}); or (3) nonproliferative diabetic retinopathy with clinically significant macular edema having hard exudates of at least grade 4. Patients with macular ischemia, pseudophakia, poorly controlled hypertension, associated vascular occlusions, media opacities, debilitating systemic diseases, coronary artery diseases and any hepatic or muscular diseases were excluded from the study, also pregnant patients were excluded. This study was conducted in Al-Azhar University Ophthalmology Department and Research Institute of Ophthalmology in Cairo in the period from July 2005 to March 2006.

After enrollment, all the patients were evaluated by an endocrinologist for control of diabetes mellitus and other metabolic factors. The protocol for our study was. In the first phase for the initial 4 to 6 weeks all 30 patients were subjected to strict metabolic control, including dietary instructions, modification of oral hypoglycemic dosage and initiation or modification of insulin dosage if required. We call this interval the metabolic control period. During the initial metabolic control period, we attempted to achieve glycosylated hemoglobin (HbAIC) concentration of <7.5%. The patients were randomized into two groups, A and B.

After randomization and during the metabolic control period, 15 patients enrolled in group A received Talbina (High dietary fibres) 50 mg day^{-1}; later, the dose was further regulated, depending on the lipid profile, with an attempt to achieve a total cholesterol concentration of 150 mg dL^{-1}, after which the patients continued to receive maintenance therapy. Liver function tests were performed for all these patients before initiating Talbina therapy. In group B, 15 patients were subjected to metabolic control but did not receive any lipid-lowering therapy.

After achieving the target metabolic control in both groups and desirable lipid profiles in group A, focal/grid laser photocoagulation of macula was done for all the eyes in both groups with Argon laser with a spot size of 100 μm with power and duration adjusted to achieve minimal gray reaction burn. Fundus photography and fluorescein angiography were done for all patients at the beginning and repeated at 6 weeks (at the end of the metabolic control period) and again at 12 and 18-week follow-up. All the patients were followed up for minimum of 18 weeks.

Lipid measurements: Serum cholesterol and triglyceride concentration were measured by enzymatic analysis by means of commercial kits (Randox Laboratories Ltd., San Francisco, California, USA). The concentration of high-density lipoprotein was measured in the supernatant after precipitation of very low density lipoprotein cholesterol and LDL cholesterol from serum using dextran sulfate and magnesium chloride. Glycosylated hemoglobin was measured by high-performance liquid chromatography.

Grading of hard exudates in fundus photographs: All patients had stereoscopic 30-degree color photographs of posterior pole taken at baseline, at 6 weeks (the end of metabolic control period), before laser photocoagulation, at 12 weeks and at 18 weeks.

The hard exudates in each standard photograph were compared with the hard exudates that were present within one disc diameter of the center of macula in the color 30-degree photograph that was being graded. The extent of hard exudates in 30-degree stereo photographs centered on the macula was based on the following scale: grade 0, no hard exudates; grade 1, questionable hard exudates; grade 2, definite hard exudates, less than standard photograph 3; grade 3, hard exudates greater than or equal to standard photograph 3 but less than standard photograph 5, grade 4, greater than or equal to standard photograph 5 but less than standard photograph 4; grade 5; greater than or equal to standard photograph 4; and grade 8, cannot grade.

All hard white or yellowish white deposits with sharp margins were included, irrespective of punctuate, confluent, or circinate pattern.

RESULTS

The study included 21 men and 9 women with non insulin-dependent diabetes. There was no significant difference between the two groups regarding the age, sex, duration of diabetes and blood pressure in the two groups (Table 1). Both groups had three patients with well-controlled hypertension each. Although the metabolic control in all the patients was variable at the time of inclusion in the study, there was no statistically significant difference between the two groups in various biochemical parameters at the baseline (Table 2). All the patients had abnormal lipid profiles at baseline.

Lipid lowering: In group A, total cholesterol concentration, LDL and triglyceride concentrations were reduced significantly after Talbina (high dietary fibre) intake (Table 3); no significant reduction was seen in group B. Serum LDL levels in group B showed a significant increase from the baseline to the 6- and 18-week intervals (Table 4). All patients in group A continued to receive Talbina until the last follow-up. None of the patients experienced any side effects, specially liver function impairment.

Patients' metabolic control was monitored by the mean HbAIC concentration, which was ≤7.5 g% throughout the study for all the patients (Table 5 and 6).

Table 1: Baseline characteristics of group A and B Patients

Characteristic	Group A	Group B	p-value
Age (year)	52.33±7.34	52.73±7.27	0.33
Sex, M.F.	10:5	11:4	>0.10
Duration of diabetes (year)	11.88±4.92	13.27±4.25	0.97
Systolic blood pressure (mm Hg)	141±7.66	142.29±3.83	0.46
Diastolic blood pressure (mm Hg)	88.11±7.59	86.95±9.32	0.73

Table 2: baseline metabolic profile of groups A and B

Investigation	Group A	Group B	p-value
Fasting blood sugar (mg dL^{-1})	169.56±49.83	174.43±55.83	0.59
Blood urea (mg dL^{-1})	48.13±12.55	42.25±14.82	0.22
Serum creatinine (mg dL^{-1})	1.13±0.520	1.16±0.420	0.85
24-h urinary proteins (g/24 h)	0.61±1.220	0.49±0.830	0.75

Table 3: Lipid profile in treatment group A

Treatments	Baseline	6 weeks	18 weeks
Serum cholesterol	237.55±33.53	203.12±25.62	180.30±26.33
Serum triglycerides	189.55±32.50	164.56±66.32	14785±52.33
Serum LDL cholesterol	129.44±62.26	109.33±35.22	101.65±34.85

LDL = Low-density Lipoprotein

Table 4: Lipid profile in treatment group B

Treatments	Baseline	6 weeks	18 weeks
Serum cholesterol	236.44±22.56	240.19±23.82	244.35±29.35
Serum triglycerides	215.52±62.53	210.34±56.36	212.65±62.39
Serum LDL cholesterol	123.32±72.28	124.36±39.11	127.45±14.95

LDL = Low-density Lipoprotein

Table 5: Distribution of hard exudates and HbA1C in treatment group A

	Grade of hard exudates at			Status of hard	Baseline HbA1C	HbA1C at 6 weeks
Patient	Baseline	6 weeks	18 weeks	exudates	(g%)	(g%)
1	5	5	5	Stablized	8.0	7.0
2	5	4	4	Stablized	8.5	7.5
3	5	5	4	Improved	8.2	7.0
4	5	4	3	Improved	9.0	7.5
5	5	5	4	Improved	9.0	7.3
6	5	5	4	Improved	8.0	6.3
7	5	3	3	Improved	8.5	7.5
8	5	4	3	Improved	8.4	7.3
9	5	5	3	Improved	7.0	7.0
10	5	4	3	Improved	7.5	7.0
11	5	5	5	Stablized	8.5	7.0
12	5	4	3	Improved	9.0	7.4
13	5	5	3	Improved	8.5	7.0
14	5	5	5	Worsened	8.6	7.0
15	5	5	3	Improved	9.0	7.0

HbA1C = Glycosylated hemoglobin

All selected eyes in both the groups had hard exudates of grade 5 or worse in the field 2. Four eyes in group A showed improvement in hard exudates by one grade within the metabolic control period(before they received laser photocoagulation). All 15 eyes in this group, including the 4 eyes that showed initial improvement, received focal photocoagulation to the microaneurysms that showed leakage on fluorescein angiography. Of the 4 eyes that had shown an improvement in the grade of hard exudates during the metabolic control period, 3 eyes continued to show

Table 6: Distribution of hard exudates and HbA1C in Treatment Group B

	Grade of hard exudates at					
Patient	Baseline	6 weeks	18 weeks	Status of hard exudates	Baseline HbA1C (g%)	HbA1C at 6 weeks (g%)
1	5	5	5	Stablized	8.0	7.0
2	5	3	2	Improved	8.5	7.0
3	5	5	5	Stabilized	7.5	7.0
4	5	5	5	Stablized	9.0	7.0
5	5	5	5	Stablized	8.5	7.0
6	5	5	5	Worsened (foveal migration)	9.0	7.3
7	5	5	5	Stablized	8.5	6.5
8	5	5	5	Worsened(foveal migration)	8.4	7.3
9	5	5	5	Stablized	8.0	7.1
10	5	5	5	Stablized	7.5	7.5
11	5	5	5	Worsened (foveal migration, subretinal fibrosis)	8.5	7.0
12	5	5	5	Worsened (foveal migration)	9.0	7.5
13	5	5	5	Stablized	7.5	7.0
14	5	5	5	Worsened	8.5	7.0
15	5	5	5	Worsened (foveal migration, subretinal fibrosis)	8.5	7.0

HbA1C = Glycosylated hemoglobin

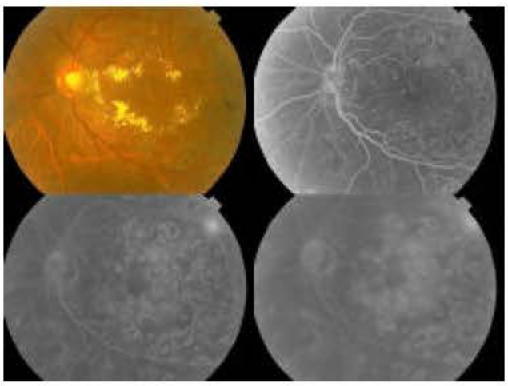

Fig. 1A: Color fundus photograph and fluorescein angiography of diabetic macular edema with hard exudates (Pre-treatment)

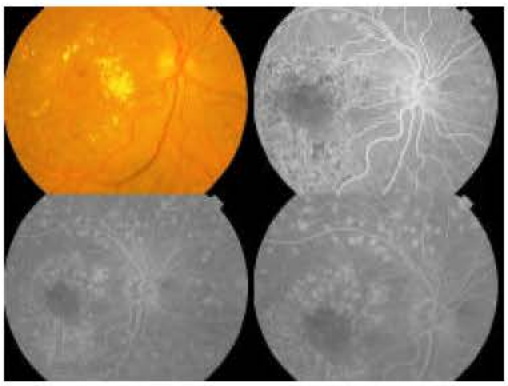

Fig. 2A: Color fundus photograph and fluorescein angiography of diabetic macular edema with hard exudates (Pre-treatment)

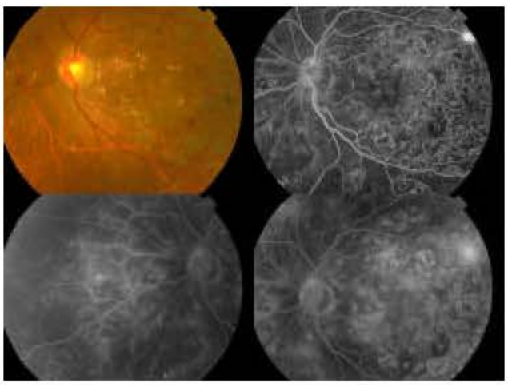

Fig. 1B: Color fundus photograph and fluorescein angiography of diabetic macular edema with hard exudates (Post-treatment)

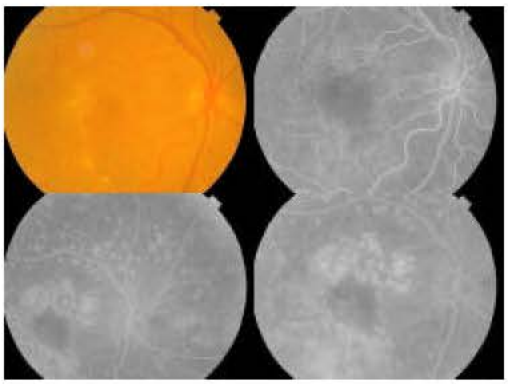

Fig. 2B: Color fundus photograph and fluorescein angiography of diabetic macular edema with hard exudates (Post-treatment)

further improvement in the grade of hard exudates during the follow-up after laser photocoagulation. The grade of hard exudates remained unchanged in other one eye. Among the remaining 11 eyes, seven showed improvement of grade during follow-up (Fig. 1 and 2) (Table 5).

Table 7: Status of hard exudates in both groups at 18-week follow-up

Status of hard exudates	Group A (n = 15), No. of eyes (%)	Group B (n = 15), No. of eyes (%)	p-value
Improved	11 (73.33)	1 (6.66)	<0.01*
Stablized	3 (20)	8 (53.33)	0.44
Worsened	1 (6.66)	6 (40)	0.08
Subfoveal migration	0	5 (33.3)	0.04*

*significantly different at p<0.005

Table 8: Status of visual acuity in both groups at 18-week follow-up

Visual acuity	Group A (n = 15), No. of eyes (%)	Group B (n = 15), No. of eyes (%)	p-value
Improved by at least two lines	5 (33.33)	3 (20)	0.67
Stablized	10 (66.66)	9 (60)	1.00
Worsened by at least two lines	---	3 (20)	0.27
Macular edema regression	9 (60.0)	5 (33.33)	0.27

In group B, only 1 eye showed improvement by grade during the metabolic control period. After focal laser photocoagulation, the grade of hard exudates improved in this eye. The status of hard exudates remained unchanged in 8 eyes and deteriorated in 6 eyes. Subfoveal lipid migration was seen in five eyes. Two of these eyes subsequently developed submacular fibrosis (Table 6 and 7).

In group A, the visual acuity remained stabilized within 2 Snellen lines of the baseline acuity in 10 eyes and improved by two or more lines in five eyes. In group B, the visual acuity remained stabilized within two lines of the baseline acuity in nine eyes, improved by two or more lines in three eyes and deteriorated by more than two lines in three eyes (Table 8). The macular edema resolved in ten eyes (66%) in group A and five eyes (33%) in group B at 18-week follow-up.

DISCUSSION

The results of our study suggest that the high dietary fibre intake (Talbina) could prove to be a useful adjunct in the management of diabetic macular edema in patients with an abnormal lipid profile. All the patients we studied had macular edema with hard exudates of grade 5 in field 2 centered on the macula. None of the patients in either group had deterioration of macular edema, visual acuity, or hard exudates in the initial metabolic control period while awaiting laser treatment, when they were subjected to metabolic control under the supervision of an endocrinologist. In fact, Four eyes in group A and One in group B showed improvement in hard exudates by at least one grade.

Hyperlipidemia is known to be associated with an increased risk of retinal hard exudates in patients with diabetes (Larson *et al*., 1999; Chew *et al*., 1996; Cohen *et al*., 1999; Biljana *et al*., 2004) Lipids presumably play an important role in causing retinal hard exudates. Increased permeability of retinal capillaries causes extravasation of less soluble plasma lipoproteins. The macrophages engulf the degenerating cells, thus resulting in the formation of a mass that is a combination of lipid-filled macrophages and extracellular lipids and is seen clinically as hard exudates (Cohen *et al*., 1999). In group A, the reduction of hyperlipidemia resulted in improvement of grade of hard exudates in four eyes even before laser photocoagulation was performed. Additionally, the reduction in hyperlipidemia in these patients seemed to enhance the reabsorption of hard exudates after laser photocoagulation. Hard exudate deposition and reabsorption is a dynamic process and these are known to absorb spontaneously (King *et al*., 1963). But it is the speckled from of small white exudates that may disappear spontaneously, within 4 months of their appearance. The circinate or the ring form of exudates that were seen in all our patients are relatively stable and their cycle of appearance and disappearance is between 2 to 3 years or longer (King *et al*., 1963). It is unlikely that four of the 15 eyes exhibited spontaneous resolution of exudates within 4 to 6 weeks, this phenomenon is most likely related to the lowering of serum lipids.

Besides laser treatment, there are a number of other factors that could actually influence the course of macular edema. One of the factors is strict metabolic control in these patients, with normalization or near normalization of blood sugar levels. However, the change in the blood sugar level matched in both groups equally and it is unlikely to have caused the beneficial effects observed in Four of the 15 patients treated with Talbina in the metabolic control period, compared with only one of the 15 patients in group B showing improvement during the same period. However, good metabolic control may still be important for causing resolution of macular edema with improvement in hard exudates. All the patients in both groups received multiple drugs for achieving metabolic control. In addition, group A patients also received Talbina (high dietary fibres). The control group was not provided any placebo because they were already receiving several drugs for metabolic control.

Hypertension is another risk factor that could have confounded the outcome results (Gupta *et al*., 1996). However, the study included only three patients in each group who had well-controlled hypertension before inclusion in the study and they continued to have their blood pressure controlled throughout the study.

The improvement in the grade of hard exudates was encouraging in the patients who received Talbina. Most of the serum cholesterol is carried to the peripheral tissue by LDL. High levels of LDL cholesterol may be toxic to

vascular endothelial cells (Tauber *et al*., 1980). Low-density lipoprotein also has a direct effect on endothelial cells, where it reduces the endothelium's ability to inhibit the platelet aggregation, thus enhancing thromboxane synthesis. Low-density lipoprotein also inhibits the release/synthesis of prostacyclin by endothelial cells of the vessel walls (Nordoy *et al*., 1978; Fleisher *et al*., 1982). The cholesterol incorporation into the platelet membranes increases the thromboxane synthesis (Stuart *et al*., 1980).

The mechanism by which fiber lowers blood cholesterol remains undefined. Evidence suggests that some soluble fibers bind bile acids or cholesterol during the intraluminal formation of micelles. The resulting reduction in the cholesterol content, of liver cells leads to an up-regulation of the LDL receptors and thus increased clearance of LDL cholesterol. However, increased bile acid excretion may not be sufficient to account for the observed cholesterol reduction. Other suggested mechanisms include inhibition of hepatic fatty acid synthesis by products of fermentation (production of short-chain fatty acids such as acetate, butyrate, propionate) changes in intestinal motility; fibers with high viscosity causing slowed absorption of macronutrients, leading to increased insulin sensitivity: and increased satiety, leading to lower overall energy intake (Anderson and Tietyen-Clark, 1986; Fedration of American Societies for Experimental Biology, 1987; Nishina and Freedland, 1990; Schneeman and Gallaher, 1985; Schneeman, 1987; Blundell and Burley, 1987).

Diabetic macular edema and the associated hard exudates are primarily a result of an underlying vascular disease. The main component of these hard exudates is believed to be cholesterol, although other lipids, such as phospholipids, may also play a role in their formation. The exudates are believed to arise because of leaky microaneurysms and capillaries; the extent of leakage actually depends on the degree of vascular permeability as well as on the level of serum lipids. Impaired retinal circulation and hyperlipidemia could both impede the reabsorption of hard exudates. Thus, lowering the serum lipid levels would help reduce the lipid leakage and its clearance. How soon the hard exudates start clearing from the retina was not determined in our study because the patients were not examined daily, but the reduction was definitely evident at the first examination performed 4 to 6 weeks after enrollment.

The hard exudates in the macula are found to be the strongest predictor of subretinal fibrosis (Fong *et al*., 1997). The reduction in the grade of hard exudates before laser photocoagulation might help in eventually reducing the development of subretinal fibrosis. Talbina (high dietary fibres) significantly reduced the risk of subfoveal lipid migration in the treatment group had subretinal fibrosis, but subfoveal lipid migration was seen in 30% and subretinal fibrosis in 13% of eyes in the control group. The short duration of treatment and late initiation of leaser treatment might have reduced the observed effects. we chose a period of 4 to 6 weeks for achieving the initial metabolic control, after which laser photocoagulation was performed. To eliminate any bias between the two groups, only patients who had HbAIC concentrations of <7.5 g% were enrolled onto the study.

The results of our study suggest that lipid-lowering therapy with high dietary fibres (Talbina) in patients with diabetes with dyslipidemia may be a useful adjunct in the management of diabetic macular edema with severe hard exudates. The results of our study are encouraging. However, our study lacks sufficient power to detect difference in visual acuity between the two groups. For determining the effect of lipid lowering in patients receiving focal and grid photocoagulation for diabetic macular edema, larger trials may be desirable, which may not be possible because lipid-lowering therapy is currently a standard of care for persons with elevated serum lipid levels, either with or without diabetes mellitus. (National Cholesterol Education Program Report of the NCEP Expert Panel on Detection, 1989; American Diabetes Association, 1995). Although our study is limited by its small sample size, the results suggest that reduction of elevated serum lipid levels may be useful adjunct to laser photocoagulation in the management of diabetic macular edema.

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