Original Article

Favorable impact of *Nigella sativa* seeds on lipid profile in type 2 diabetic patients

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ABSTRACT

Background and Aim: The atherogenic pattern of dyslipidemia associated with type 2 diabetes mellitus (DM) has been increasingly discussed. We have recently reported a hypoglycemic effect of *Nigella sativa* (NS) seeds in patients with type 2 DM. In this study we sought to assess the impact of NS seeds on lipid profile in type 2 diabetic patients. **Patients and Method:** A total of 94 patients with type 2 DM were recruited and divided into 3 dose groups. Capsules containing NS were administered orally in a dose of 1, 2, and 3 g/day for 12 weeks. All patients were subjected to measurement of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) before treatment and 4, 8, and 12 weeks thereafter. **Results:** Patients receiving 1 g/day NS seeds for 12 weeks (group 1) showed nonsignificant changes in all the parameters except for a significant increase in HDL-c after 4 weeks of treatment. However, patients ingested 2 g/day NS displayed a significant decline in TC, TG, and LDL-c, and a significant elevation in HDL-c/LDL-c, compared with their baseline data and to group 1 patients. Increasing NS dose to 3 g/day failed to show any increase in the hypolipdemic effect produced by the 2 g/day dose. **Conclusion:** NS supplementation at a dose of 2 g/day for 12 weeks may improve the dyslipidemia associated with type 2 diabetic patients. Therefore, NS is a potential protective natural agent against atherosclerosis and cardiovascular complications in these patients.

Key words: Black seeds, diabetes mellitus type 2, dyslipidemia, HDL, LDL, *Nigella sativa*, total cholesterol, triglycerides

INTRODUCTION

Diabetes mellitus (DM) is the most common metabolic disorder worldwide. Patients with type 2 DM have a complex alteration in plasma lipids characterized by elevated level of triglycerides (TG), decreased level of high-density lipoprotein cholesterol (HDL-c), and a preponderance of small dense low-density lipoprotein cholesterol (LDL-c).[1,2] The abnormalities in circulating lipids and lipoproteins are considered to be important risk factors for cardiovascular disease in diabetic individuals.[3,4] Reversal of these abnormalities in lipid profile may reduce the accelerated atherosclerosis and the related macrovascular complications in patients with DM.[5]

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Nigella sativa (NS) is an annual herbaceous plant belonging to the family Ranunculaceae.[6] We have recently demonstrated an improvement in glycemic control and insulin resistance in type 2 diabetic patients induced by NS treatment.[7] The hypolipidemic effect of NS has been demonstrated, earlier, in experimental animals. These studies reported that NS has a favorable effect on TG and lipoprotein pattern in normal rats.[8-10] Similar findings were encountered by the administration of thymoquinone, the active ingredient of NS, to rabbits fed on cholesterol-enriched diet,[11] and to hypercholesterolemic rats.[12] Interestingly, the effect of NS on lipid profile in humans is controversial. Earlier study on healthy human volunteers ingested powdered NS for 2 weeks, reported a fall in plasma cholesterol level in the first week and a rise thereafter,[13] while another study indicated that oral NS seed extract supplemented in patients with mild hypertension for 8 weeks, caused a significant decline in levels of total cholesterol (TC) and LDL-c, relative to baseline data.[14] On the other hand, nonsignificant favorable impact of NS on serum lipids was detected in human adults[15] and

in central obese men.[16] However, literature is lacking data on the lipid-lowering potential of NS in diabetic patients. Therefore, this study was carried out to evaluate the effect of NS on lipid profile in patients with type 2 DM as a secondary objective for studying its hypoglycemic effects, which was reported earlier.[7]

MATERIALS AND METHODS

Patient selection

The study was conducted on 94 patients (43 males and 51 females) with uncontrolled type 2DM. Patients in the study were recruited from King Fahd Hospital of the University and Al-Aqrabia Primary Health Care Center, Al-Khobar, Saudi Arabia, in the period between January 2008 and February 2009. DM was diagnosed according to the latest diagnostic criteria of the American Diabetes Association.[17] The selection of uncontrolled diabetes was made on the basis of two successive readings of HbA_{1c} more than 7%, done 3 months apart. Patients included were of age 18–60 years, treated with oral hypoglycemic agents (glipenclamide, metformin, rosiglitazone), had no change in the dose of lipid-lowering agents over the last 8 weeks, and ready for regular follow-up. Patients were excluded if the serum triglyceride was >400 mg/dL, if they had cardiac illness (ischemic heart disease, heart failure, and cardiac arrhythmias), liver disease (active hepatitis and liver cirrhosis), renal impairment, or secondary cause of dyslipidemia. Patients were also excluded if they had compliance < 90% to NS and if their standard medications were changed during the 12 weeks of the study. Pregnant and lactating women were also excluded. All patients were fully informed about the purpose and duration of the study and they were free to leave the study at any time. The treatment with NS was planned to be stopped in case of observation of adverse event. Written informed consent was obtained from all the participants. The study has been approved by the research ethics committee of King Faisal University, Dammam, reference number KFU-LEC-132.

Study design

This is a prospective, open-label, second-phase trial, which was conducted as part of studying the hypoglycemic effect of NS in patients with type 2 DM. Recruited patients fulfilling the above-mentioned criteria were divided into 3 groups through simple random sampling and were administered 3 different oral doses of NS (1 g, 2 g, and 3 g per day for 12 weeks). NS seeds (Bioextract (Pvt) Ltd, Sri Lanka) were provided in the form of 500 mg capsules of grounded NS (powder). All patients in the 3 groups were subjected to history taken, physical examination, and laboratory investigations.

Investigations including TC, TG, LDL-c, and HDL-c were done for all patients before initiation of treatment (baseline) and 4, 8, and 12 weeks thereafter. During the first 2 weeks of administration of NS, patients were contacted daily by telephone, and were enquired about any new symptoms. They were also asked to report any change in their medication or lifestyle. Patients were seen in the clinic every 4 weeks and compliance to NS over the whole study period was ensured through capsules count. Patients were not provided with any specific dietary instructions and were asked to continue the same diet they used to take before the study.

Data analysis

Change in TC, TG, LDL-c, and HDL-c levels, in addition to changes in HDL-c/LDL-c ratio and HDL-c/TC ratio, measured at 4, 8, and 12 weeks after intervention, was taken as secondary endpoint of studying the effect of NS on glycemic control. Blood samples were collected, after at least 12 h of fasting, into plain tubes (without anticoagulant) and allowed to clot. It was, then centrifuged at 3000 rpm for 8 min for separation of the serum. Serum was stored and kept frozen at -20°C for up to 1 week until used for determination of TC, TG, and HDL-c, using kits, supplied by Dade Behring, Germany. Assays were performed according to the manufacturer's instructions, using the automated assay analyzer (Dimension Clinical Chemistry System, Germany). LDL-c was calculated using the Friedewald formula.[18]

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS) version 11. Data were presented as mean ± standard error of the mean (SEM). All experimental results were compared with their own baseline values by paired Student's *t* test. The corresponding parameters in the 3 groups were, also, compared by means of a one-way analysis of variance (ANOVA) test followed by least significant difference (LSD) multiple range-test to find intergroup significance. A probability of $P < 0.05$ was considered significant.

RESULTS

Among the 94 patients recruited, 13 were excluded due to compliance of less than 90% to NS treatment, 7 patients were excluded due to change in the antidiabetic medications, and 3 lost to follow up. None of the studied individuals had side effects that necessitated the discontinuation of NS. Table 1 represents the baseline characteristics of the study population. The mean age was 47.80 ± 1.42, 49.63 ± 0.97, and 44.91 ± 1.88 years for groups 1, 2, and 3, respectively. Age and duration of diabetes were not significantly different between the 3 groups, except for age that was significantly lower in group 3 compared with group 2.

Table 1: No of patients, age, duration of diabetes, dose of *Nigella sativa*, and duration of supplementation in 3 groups of patients with type 2 diabetes mellitus

	Group I	Group II	Group III
No. of patients	30 (16 females)	32 (18 Females)	32 (17 females)
No. of patients excluded	7	6	10
Age (years) Mean ± SEM	47.80 ± 1.42	49.63 ± 0.97	44.91 ± 1.88
Duration of diabetes (years) mean ± SEM	7.9 ± 1.02	7.12 ± 0.92	6.74 ± 1.08
Dose of *N. sativa*	500 mg twice daily (1 g/day)	1 g twice daily (2 g/day)	1 g thrice daily (3 g/day)
Duration of *N. sativa* supplementation	12 weeks	12 weeks	12 weeks

SEM, Standard error of mean; Age and duration of diabetes were nonsignificantly different between the 3 groups, except for age that was significantly lower in group 3 compared with group 2, using ANOVA.

Table 2 displays the changes in lipid profile in the 3 groups of diabetic patients supplied with NS (1, 2, and 3 g/day for 12 weeks), compared with their corresponding baseline values. Group 1 patients, treated with 1 g/day NS, showed nonsignificant changes in TC, TG, and LDL-c throughout the duration. HDL-c increased in all time points of NS supplementation, yet the increment was only significant in the fourth week reading. The ratios of HDL-c to LDL-c and to TC did not change significantly, compared with the baseline values. Patients treated with 2 g/day NS for 12 weeks showed a significant drop in both TC and TG levels, starting from the fourth week of treatment and maintained thereafter. TC decreased by 11.3%, 15.2%, and 11.1% and TG reduced by 20.0%, 17.4%, and 22.2%, after 4, 8, and 12 weeks of treatment, respectively, compared with their corresponding baseline values. Also, the levels of LDL-c declined significantly by 16.3%, and 16.8% after 8 and 12 weeks, respectively. However, the levels of HDL-c were maintained throughout the treatment duration. Interestingly, the ratio of HDL-c to LDL-c was significantly elevated after 8 and 12 weeks and the HDL-c ration to TC was also elevated significantly in all of the 3 readings obtained. On the other hand, 3 g/day NS supplementation for 12 weeks (group 3) was not as potent as the 2 g dose. The only significant change produced by this dose was on TC, which was reduced in the 4th and 12th week readings. All other parameters did not change significantly, although they had the same trend as the 2 g dose.

Figures 1 and 2 illustrate the changes in lipid profile in the 3 groups compared with each other by ANOVA. TC levels significantly decreased after 4 and 12 weeks of treatment in groups 2 and 3 as compared with group 1. Moreover, there was a decrease in TG levels in groups 2 and 3, compared with group 1, throughout the treatment period, yet the decline was only significant for group 2. Furthermore, LDL-c levels in group 2 significantly decreased after 8 and 12 weeks of treatment compared with group 1, and only after 8 weeks compared with group 3. In contrast, HDL-c/LDL-c ratio significantly increased after 8 and 12 weeks of treatment, in group 2 compared with group 1, whereas HDL-c level and HDLc/TC ratio did not differ significantly between the 3 groups.

DISCUSSION

The results show a promising hypolipidemic effect produced by 2 g/day NS supplementation in type 2 diabetic patients. It has been reported that LDL-c positively and HDL-C negatively correlates with cardiovascular disease.[19] Circulating LDL-C can pass from the blood into the arterial wall where it may be oxidized and engulfed by macrophages forming foam cells. Thereafter, a complex interplay of cell necrosis, smooth muscle recruitment, and collagen deposition leads to the development of atherosclerotic plaques. However, HDL-c possesses antioxidant and anti-inflammatory activities and promotes the efflux of cholesterol from the peripheral tissues to the liver, thereby reducing the uptake of cholesterol by macrophages and providing a protective effect against atherosclerosis.[20] Therefore, to reduce the risk of cardiovascular disease, many strategies have been adopted to decrease the circulating LDL-c level and increase HDL-c level.[21]

Our study demonstrated a decrease in TC, TG, and LDL-c levels and an increase in the ratios of HDL-c to LDL-c and to TC with daily ingestion of 2 g NS. Taken together, these quantitative and qualitative changes in lipid profile monitor an improvement in the dyslipidemia in diabetic patients receiving 2 g/day NS. The reduction in LDL-c, besides the elevation in ratios of HDL-c to LDL-c and to TC indicates a useful transfer of cholesterol, among lipoprotein particles in favor of an antiatherogenic shift in their profile. Even, the decrease in LDL-c is sufficiently enough predictor for the beneficial effect of NS on lipid pattern; American Diabetic Association has identified LDL-c as the primary target of lipid lowering in diabetic dysfunction.[22] These findings seem to be in agreement with the results of previous studies carried out on human beings, demonstrating a marginal reduction in TC after

Table 2: Mean ± SEM of triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HDL-c/LDL-c ratio, and HDL-c/TC ratio, in type 2 diabetic patients, treated with *Nigella sativa* 1 g/day (group 1), 2 g/day (group 2), and 3 g/day (group 3), for 12 weeks, compared with the corresponding baseline values

Parameter	Group 1				Group 2				Group 3			
	Baseline values	Treatment duration in weeks			Baseline values	Treatment duration in weeks			Baseline values	Treatment duration in weeks		
		4	8	12		4	8	12		4	8	12
TG (mg/dL)												
Mean ± SEM	126.05 ± 12.83	124.28 ± 9.72	131.37 ± 17.74	134.84 ±19.46	191.76 ± 27.10	153.32 ± 23.23	158.37 ± 30.88	149.18 ± 22.75	215.67 ± 26.24	209.31 ± 27.27	182.44 ± 22.42	176.11 ± 21.82
n (%)	22	22 (1.4)	19 (4.22)	19 (6.97)	25	25 (20)	19 (17.4)	22 (22.2)	18	16 (3)	16 (15.4)	18 (18.3)
P		NS	NS	NS		<0.004	<0.001	<0.01		NS	NS	NS
TC (mg/dL)												
Mean ± SEM	166.55 ± 7.55	172.41 ± 7.93	167.95 ± 10.15	174.47 ± 8.74	195.24 ± 7.38	173.12 ± 7.74	165.63 ± 8.44	173.50 ± 10.44	208.17 ± 8.45	175.56 ± 8.96	193.06 ± 11.03	185.94 ± 8.26
n (%)	22	22 (3.39)	19 (0.84)	19 (4.75)	25	25 (11.3)	19 (15.2)	22 (11.1)	18	16 (15.7)	16 (7.3)	18 (10.7)
P		NS	NS	NS		<0.010	<0.002	<0.04		<0.03	NS	<0.01
LDL-c (mg/dL)												
Mean ± SEM	107.31 ± 8.34	110.19 ± 8.69	114.00 ± 9.79	112.17 ± 11.32	125.84 ± 8.67	113.05 ± 6.73	105.29 ± 6.78	104.71 ± 9.37	131.73 ± 11.44	116.30 ± 8.54	137.90 ± 13.49	124.9 ± 14.08
n (%)	16	16 (2.86)	13 (6.23)	12 (4.23)	19	19 (10.1)	15 (16.3)	17 (16.8)	11	10 (11.7)	11 (4.7)	11 (5.2)
P		NS	NS	NS		NS	<0.01	<0.04		NS	NS	NS
HDL-c (mg/dL)												
Mean ± SEM	38.19 ± 2.28	40.19 ± 1.92	39.23 ± 2.19	40.33 ± 2.80	43.94 ± 3.45	46.58 ± 2.81	43.00 ± 2.97	45.35 ± 3.35	36.27 ± 2.07	38.30 ± 3.21	39.00 ± 2.39	39.81 ± 2.53
n (%)	16	16 (5.24)	13 (2.72)	12 (5.3)	19	19 (6)	15 (2.1)	17 (3.2)	11	10 (5.6)	11 (7.5)	11 (9.8)
P		<0.04	NS	NS		NS	NS	NS		NS	NS	NS
HDL-c/LDL-c												
Mean ± SEM	0.37 ± AQ30.02	0.41 ± 0.04	0.36 ± 0.02	0.39 ± 0.04	0.38 ± 0.03	0.44 ± 0.04	0.42 ± 0.03	0.47 ± 0.04	0.30 ± 0.3	0.34 ± 0.03	0.30 ± 0.03	0.37 ± 0.64
n (%)	16	16	13	12	19	19	15	17	11	10	11	11
P		NS	NS	NS		NS	<0.01	<0.02		NS	NS	NS
HDL-c/TC												
Mean ± SEM	0.23 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.23 ± 0.01	0.23 ± 0.02	0.26 ± 0.02	0.26 ± 0.02	0.28 ± 0.02	0.18 ± 0.02	0.21 ± 0.02	0.21 ± 0.27	0.22 ± 0.03
n (%)	16	16	13	12	19	19	15	17	11	10	11	11
P		NS	NS	NS		<0.02	<0.003	<0.01		NS	NS	NS

LDL-c, Low-density lipoprotein cholesterol; HDL-c, High-density lipoprotein cholesterol; n, Number of patients; NS, Not significant; %, percentage of change from baseline value; SEM, Standard error of mean; TC, Total cholesterol; TG, Triglycerides. *P*, Significance of difference from baseline values, using Student's t test, for paired data.

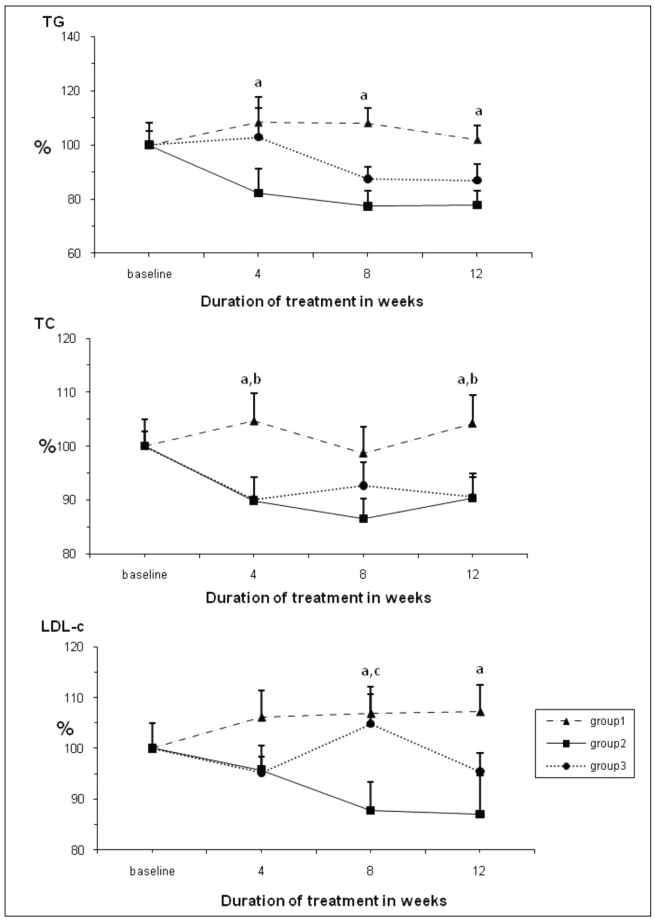

Figure 1: Changes in triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) in type 2 diabetic patients received 1 g/day (group 1), 2 g/day (group 2), and 3 g/day (group 3) of *Nigella sativa* for 12 weeks. The corresponding parameters in the 3 groups were compared using analysis of variance. Data are mean ± standard error of mean of the values as percentages of the corresponding baseline values, considering baseline values equal 100. (a) Significance of difference between groups 2 and 1 ($P < 0.05$), (b) significance of difference between groups 3 and 1 ($P < 0.05$), and (c) significance of difference between groups 2 and 3 ($P < 0.05$)

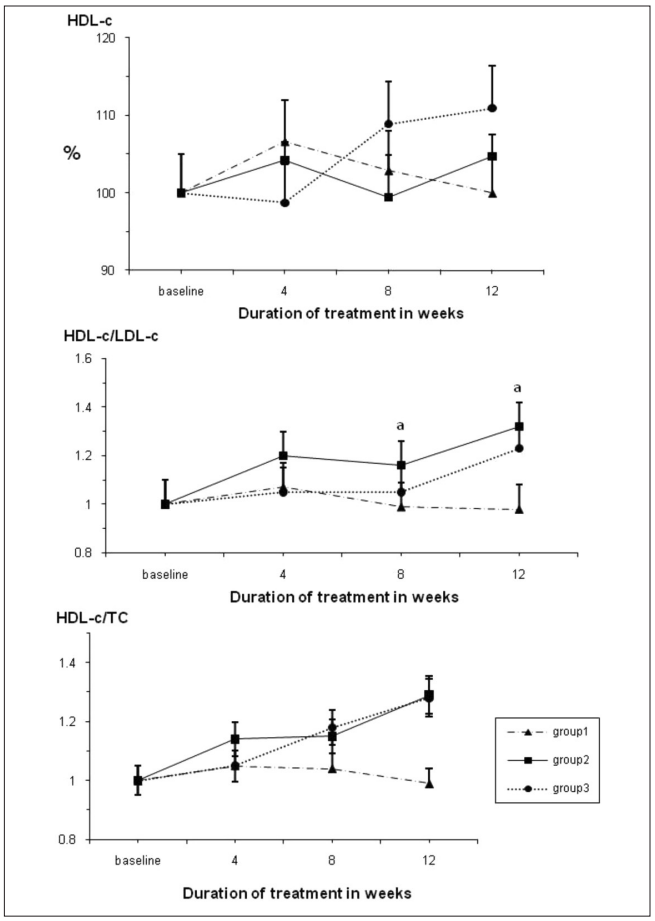

Figure 2: Changes in high-density lipoprotein cholesterol (HDL-c) and ratios of HDL-c to low-density lipoprotein cholesterol (HDL-c/LDL-c ratio) and to total cholesterol (HDL-c/TC ratio), in type 2 diabetic patients received 1 g/day (group 1), 2 g/day (group 2), and 3 g/day (group 3) of *Nigella sativa* for 12 weeks. The corresponding parameters in the 3 groups were compared using analysis of variance. Data are mean ± standard error of mean of the values as percentages of the corresponding baseline values, considering baseline values equal 100. (a) Significance of difference between groups 2 and 1 ($P < 0.05$). Group 3 was nonsignificantly different from groups 1 and 2

1 week of daily treatment with 2 g/day NS seeds,[13] and a slight reduction in TG and a discrete elevation in HDL-c following administration of NS oil for treatment of allergic diseases.[23] Other investigators reported nonsignificant favorable impact on serum lipid after NS supplementation in adults[15] and in central obese men.[16] Meanwhile, the favorable impact of NS on the serum lipid pattern detected, herein, confirm the hypolipidemic effect of NS demonstrated earlier in normal rats[8,9,24] and in streptozotocin-induced diabetic rats.[25]

Interestingly, the doses used in this study covered the anticipated effect of the drug on the parameters studied. While 1 g NS was unable to produce significant hypolipidemic effect, the 2 g was enough to do so. However, the 3 g was even less potent than the 2 gram in its lipid-lowering effect. This could be partly due to less compliance of patients in the higher dose group, which made its "n" values, in many parameters, smaller. Another possible cause, for the less effect for the 3 g dose, is the presence of other ingredients in the NS seeds that may produce a counter-acting effect at this higher dose. The same phenomena of less effect, than expected, by the 3 g dose have been encountered in our previous report on the hypoglycemic effect of NS.[7] Furthermore, the 3 g dose of NS was less potent than the 2 g in eradicating *Helicobacter pylori* in nonulcer dyspeptic patients.[26]

No obvious mechanism is available to explain the antiatherogenic pattern of lipoprotein profile found in the present study following NS supplementation. However, improvement in insulin resistance in type 2 diabetic patients receiving NS seeds[7] may be, partly, implicated. Jin *et al*[27] related the decrease in TG and LDL-c and the

increase in HDL-c to improvement in insulin resistance following tangzhiping granules supplementation in rat model of insulin resistance type 2 diabetes. Annuzzi *et al*.[28] concluded that insulin resistance is associated with postprandial lipoprotein abnormalities in type 2 diabetic patients after acute correction for hyperglycemia and hyperinsulinemia. Moreover, the atherogenic pattern of dyslipidemia, associated with type 2 DM, has been reported to result from insulin resistance that leads to the release of free fatty acids from adipose tissue, increased hepatic production of very–low-density lipoproteins and decreased high-density lipoproteins.[29] Oxidative stress and reactive oxygen species are now accepted as a likely causative factor in the development of insulin resistance.[30,31] Thymoquinone, the active constituent of NS has been demonstrated to attenuate oxidative stress in streptozotocin-induced diabetic rats,[32] and in hypercholesterolemic rats.[12] Kaleem *et al*.[25] confirmed the antidiabetic activity of NS and its efficiency in controlling the dyslipidemia, linking these actions to its antioxidant effects. Therefore, the antioxidant activity of NS may, also, be implicated in ameliorating the dyslipidemia associated with diabetes through decreasing insulin resistance.

The main strength of this study comes from being the first attempt to evaluate the effect of NS on the lipid profile in patients with type 2 DM. However, this study has some limitations, such as the small sample size in each of the study groups, being open-label study, and the lack of placebo-control group. In conclusion, administration of 2 g/day NS seeds may be effective in lowering blood lipids and producing an antiatherogenic lipoprotein pattern in patients with type 2DM. Further blinded, placebo-controlled clinical trials are needed to support current promising results and to explore the exact underlying mechanism(s) of NS effects on lipid profile.

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