

THERAPEUTIC EFFECT OF NIGELLA SATIVA IN PATIENTS OF POOR GLYCEMIC CONTROL

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ABSTRACT

Objective: This study evaluated the effects of *Nigella sativa* on the glycemic control in patients of metabolic syndrome with poor glycemic control (HbA1C > 7 %). Various parameters used to study about glycemic control were glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PPBG)

Material & Methods: Eighty Patients (80) were randomly divided into two groups (n=40 each) through random stratification by weight. In group I (Std), patients were advised metformin 500 mg twice a day & atorvastatin 10 mg once a day for a period of eight weeks. In group II (NS) patients were advised recommended doses of *Nigella sativa* (NS) in addition to abovementioned drugs. Aspirin 150 mg was given in both groups. Each subject's FBG, PPBG & HbA1c was measured at the beginning of the study, then once every two weeks during the study. Venous blood was also collected from each subject before and after the intervention for lipid profile.

Results: *Nigella sativa* significantly lowered FBG, PPBG & HbA1c after 8 weeks. The NS group showed significant improvement with reference to FBG, PPBG, HbA1c, and LDL-cholesterol.

Conclusions: *Nigella sativa* can be used as add on drug therapy in metabolic syndrome patients with poor glycemic control. *Nigella sativa* is safe and an effective remedy in patients of metabolic syndrome.

Keywords: *Nigella sativa*, Poor glycemic control, Glycated hemoglobin (HbA1C)

INTRODUCTION

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) that is deserving of more clinical attention. It is difficult to achieve proper glycemic control in patients of metabolic syndrome. Most of the time combinations of oral hypoglycemic drugs are used to achieve proper glycemic control. Proper glycemic control can prevent micro and macrovascular complication of diabetes like stroke, coronary heart disease, retinopathy and nephropathy etc. The etiology, prevention and treatment of the metabolic syndrome are currently the focus of intense research activities. The metabolic syndrome seems to have three potential etiological categories: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (e.g., molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well. Out of abovementioned three factors, insulin resistance is the key abnormality in patients of metabolic syndrome. Alternative medicine has opened new door for the treatment of cardiometabolic disorders which has attained epidemic proportion throughout the world. *Nigella* (Kalonji) (*Nigella sativa*) belonging to the buttercup family Ranunculaceae, is commonly known as black seeds. *Nigella* seeds have many pharmaceutical uses. The seeds have occupied special place for their medicinal value for centuries in the Middle East and Southeast Asia¹. *Nigella sativa* seed, used for centuries for medicinal and culinary purposes and reported to possess a number of pharmacological properties, including antioxidant², anti-inflammatory³, hypoglycemic⁴, antihypertensive⁵ and antihyperlipidemic⁶ properties. Our aim is to study the effect of *Nigella sativa* on the blood pressure in patients of metabolic syndrome

MATERIAL AND METHODS

The present study was conducted on newly detected patients of metabolic syndrome with poor glycemic control (HbA1C >7 %) in a teaching Hospital of North India from October 2005 to March 2007. The study group comprised of 80 patients of metabolic syndrome. There were 52 males and 38 females. The age group of the patients varied from 20 years to 70 years but majority of the patients were in 40-60 years age group. After final diagnosis and considering inclusion and exclusion criteria patients were enrolled in this prospective study. Approval from institutional ethical

committee was taken. The participants were informed of all possible expected benefits and possible harm ensuing from the study. Written consent was obtained from the study subjects. This was an open label randomized controlled study. These patients were diagnosed as having metabolic syndrome with type II diabetes mellitus according to ATP III criteria. We had taken patients of metabolic syndrome with poor glycemic control (HbA1C > 7 %). The exclusion criteria were pregnancy, type I diabetes mellitus, acute coronary syndromes and cerebrovascular accidents, impaired liver function test, Patients of chronic renal disease, familial dyslipidemia. Eighty (80) patients were randomly divided into two groups (n=40 each). In group I (Std group), patients were advised metformin 500 mg twice a day and atorvastatin 10 mg once a day for a period of eight weeks. In group II (NSO group) patients were advised abovementioned drugs and 500 mg capsule of *Nigella sativa* as add on therapy. Aspirin 150 mg once a day was given in both groups.

N. sativa seeds of indigenous variety were obtained from a local herbal market Aligarh. *N. sativa* seeds were authenticated. Then the seeds were washed, dried and crushed to a powder with an electric microniser. Five hundred milli gram capsules were made by this powder. After collecting base line data of glycemic control and lipid profile, a dose of two month *Nigella sativa* capsules (60 capsules) was given to patients in group II and were asked to use capsules regularly

Each subject's glycemic control was measured by recording FBG, PPBG & HbA1C at the beginning of the trial, then once every two weeks during the trial. Venous blood was also collected from each subject before and after the trial. Blood samples were assayed for serum lipid profiles. Advices about dietary and lifestyle changes were given to both *Nigella sativa* and standard groups. After informed consent was obtained, blood samples were drawn after an overnight fast at baseline and after two months of intervention. For the determination of HbA 1c EDTA blood was used. HbA 1c was assessed by immunoturbidimetric determination (Roche- Tinaquant Roche Diagnostics, Mannheim). Fasting plasma glucose was measured by the hexokinase method.

STATISTICAL ANALYSIS

Pre and post intervention mean \pm standard deviation of each parameter was calculated for both groups. Paired t test was applied to know the intragroup difference of each variable before and after intervention. Then unpaired t test was applied to know about

intergroup difference between both groups All the statistic were done by using 13 th version of SPSS software. Owing to the skewed distribution of triglyceride concentrations the Mann-WhitneyU -test was applied for detection of intergroup differences and the Wilcoxon test for intragroup differences for this variable. Correlation between fasting plasma glucose levels at baseline and the absolute differences of fasting glucose were analyzed with the Pearson method. *P* -values < 0.05 were considered statistically significant.

RESULTS

Both intergroup and intragroup reduction in FBG, PPBG, HbA1C, and LDL was significantly more (*P* value < 0.001) in NS group as compared to Std group. Both intergroup and intragroup reduction in TG was significantly more (*P* value < 0.001) in Std group as compared to NS group. HDL was increased in both Std and NS group but neither intragroup nor intergroup difference was significant (*P* value 0.122). No adverse effects were reported by participants during the study. Table one shows mean \pm SD of different parameters before and after intervention in both groups. Table two shows postintervention mean \pm SD of both groups

Table 1: Variables of glucose and lipid metabolism at baseline and after the intervention period in both groups

Parameters	Before Intervention (Mean \pm SD)	After Intervention Mean \pm SD
FBG (Std)	144.2683 \pm 21.6042	135.6951 \pm 11.6414
FBG (NS)†	165.5823 \pm 32.5772	144.3411 \pm 12.9111
PPBG (Std)	220.5000 \pm 33.8553	198.0886 \pm 17.5751
PPBG (NS)†	238.9241 \pm 53.8271	199.3902 \pm 27.3605
HbA1C (Std)	7.71 \pm 0.73	7.18 \pm 0.70
HbA1C (NS)†	8.11 \pm 0.83	6.99 \pm 0.83
TG (Std)†	233.5244 \pm 32.7060	155.0122 \pm 16.9724
TG(NS)	195.7595 \pm 65.8881	150.3924 \pm 38.9172
LDL (Std)	139.2805 \pm 16.6439	128.2405 \pm 12.5820
LDL (NS)†	163.6835 \pm 32.2154	117.8780 \pm 20.4107
HDL (Std)	43.1463 \pm 5.4209	45.6829 \pm 7.9378
HDL (NS)	44.0127 \pm 4.2892	46.6203 \pm 6.4456

*Data are mean \pm SD

†Significantly different from baseline (*P* < 0.001).

Table 2: Post intervention mean \pm SD of standard (group I) and nigella sativa group (group II)

Parameter	Post intervention Mean \pm SD of Std Group (n=40)	Post intervention Mean \pm SD of group(n=40) NSO
FBG‡	135.6951 \pm 11.6414	144.3411 \pm 12.9111
PPBG‡	198.0886 \pm 17.5751	199.3902 \pm 27.3605
HbA1C‡	7.18 \pm 0.70	6.99 \pm 0.83
TG	155.0122 \pm 16.9724	150.3924 \pm 38.9172
HDL	45.6829 \pm 7.9378	46.6203 \pm 6.4456
LDL‡	128.2405 \pm 12.5820	117.8780 \pm 20.4107

Data are mean \pm SD.

‡ Significantly different from the standard group (*P* value < 0.001)

DISCUSSION

To our knowledge this is the first study evaluating the effect of Nigella sativa on FBG, PPBG, HbA1C & lipid profile of metabolic syndrome patients with poor glycemic control (HbA1C > 7 %). Reduction in FBG, PPBG, HbA1C were more (*P* value < 0.001) in Nigella sativa group as compared to standard group Significant improvement in HbA1C indicates that Nigella sativa can be used as add on therapy to those patients whose glycemic control cannot be achieved by conventional drugs. Combinations of oral hypoglycemic drugs are used to achieve glycemic control. For this hypoglycemic drugs like sulfonylurea are combined with insulin sensitizers like metformin or thiazolidinediones. With the labeling of tolbutamide by the U.S. Food and Drug Administration in 1962, the sulfonylurea class of drugs quickly became the mainstay of treatment for type 2 diabetes. Although newer agents have recently entered the

marketplace, sulfonylureas still play a primary role in pharmacologic management of type 2 diabetes. Patients who respond best to treatment with sulfonylureas include those with a diagnosis of type 2 diabetes before 40 years of age, duration of disease less than five years before initiation of drug therapy and a fasting blood glucose level of less than 300 mg per dL. Approximately two thirds of patients who begin therapy with a sulfonylurea respond, although up to 20 percent of them eventually require additional medication. Few patients with uncontrolled diabetes receive clinical benefit when switched from one sulfonylurea agent to another. The use of agents with a longer half-life e.g., chlorpropamide in the elderly and in patients with renal impairment is discouraged because the risk of hypoglycemia is increased.

We had taken metformin because of certain advantages. Metformin is a biguanide agent that lowers blood glucose primarily by decreasing hepatic glucose output and reducing insulin resistance. When used as monotherapy, metformin does not cause hypoglycemia and is thus termed an "antihyperglycemic". The reported incidence of lactic acidosis during metformin treatment is less than 0.1 cases per thousand patient years and the mortality risk is even lower. Metformin does not promote weight gain and can reduce plasma triglyceride by 15 % to 20 %.Metformin is the only therapeutic agent that has been demonstrated to reduce macrovascular events in type 2 diabetes mellitus⁷ The Diabetes Prevention Program demonstrated the effectiveness of lifestyle change in persons with impaired fasting glucose, but metformin hydrochloride was also effective in delaying progression to overt diabetes in patients with impaired fasting glucose⁸

The thiazolidinediones are a unique drug class of "insulin sensitizers" that promote skeletal muscle glucose uptake Troglitazone is the first agent of this drug class to be introduced in the U.S. market and, like metformin, it reduces insulin resistance. Troglitazone is beneficial in patients requiring large daily amounts of insulin (more than 30 units per day) whose diabetes is still uncontrolled. A reduction of up to 50 percent in total daily insulin dosage is possible with drug titration. Troglitazone is also effective when used in combination with other oral agents thereby potentially delaying the need to start insulin therapy. The U.S. Food and Drug Administration recently ruled that troglitazone should only be used in combination with other diabetic therapies. Over 150 case reports of hepatotoxicity have been reported with troglitazone, so liver function must be monitored every month for the first eight months of treatment and every other month for four months thereafter. Periodic transaminase measurements should be obtained as long as the patient is taking troglitazone.

The various mechanisms proposed for its hypoglycemic activity of Nigella sativa were insulin sensitizing action⁹ and stimulatory effect on beta cell function⁸. In view of the folkloric use of plant mixture extracts for treatment of diabetes in the Middle East, Al-Awadi and Gumaa¹⁰ studied a plant mixture (Nigella sativa, Myrrh, Gum olibanum and Gum asafoetida) for its blood glucose lowering effect in rats and found it effective. Further studies on the plant mixture containing N. sativa; revealed that the blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis and the plant extract mixture may prove to be a useful therapeutic agent in the treatment of non-Insulin dependent diabetes mellitus. An aqueous decoction of a plant mixture containing Nigella sativa was found to lower the blood glucose level significantly⁹. Administration of volatile oil of N. sativa seeds produced a significant hypoglycemic effect in normal and alloxan-induced diabetic rabbits¹⁰. The hypoglycemic effects of Nigella sativa in combination with other herbs has also been demonstrated in a study on alloxan-induced diabetic rats. In another study, the seed extract when given orally decrease the elevated glucose levels in alloxan-induced diabetic rabbits after 2 months of treatment. Another study was designed to investigate the possible insulinotropic properties of Nigella sativa oil in Streptozotocin plus Nicotinamide-induced diabetes mellitus in hamsters. After eight weeks of treatment with N. sativa, significant decrease in blood glucose level together with significant increase in serum albumin level were observed. The results showed that the hypoglycemic effect of N. sativa oil was, at least partly; because of a stimulatory effect on beta cell function with consequent increase in

serum insulin level and possess insulinotropic properties in type II like model¹¹. In another study, the hypoglycemic effect of *Nigella sativa* was supposed to be mediated by extra pancreatic actions rather than by stimulated insulin release. El-Dakhakhny et al¹³ (2000) studied the effect of seed oil on blood glucose concentrations in Streptozotocin-induced diabetic rats. The effect of seed oil and other constituents such as nigellone and thymoquinone were studied on insulin secretions of isolated rat pancreatic islets in the presence of 3, 5.6 or 11.1 mM glucose. Oil significantly lowered the blood glucose concentrations in diabetic rats after 2, 4 and 6 weeks, which was, however, not paralleled by a stimulation of insulin release in the presence of oil, nigellone or thymoquinone; thus indicating the extra pancreatic actions to be responsible for hypoglycemic effects of *Nigella sativa* oil. A recent clinical study on human volunteers showed that 1 g of *N. sativa* seeds twice daily caused a decrease in blood glucose level after 2 weeks of oral treatment. In a clinical study *N. sativa* seed powder given with Karela (*Momordica charantia*) to NIDDM patients was found to be hypoglycemic¹³.

Kanter M et al¹⁴ studied the possible protective effects of *Nigella sativa* L. (NS) against beta-cell damage from streptozotocin (STZ)-induced diabetes in rats. They found that NS treatment exerts a therapeutic protective effect in diabetes by decreasing oxidative stress and preserving pancreatic beta-cell integrity. Consequently, NS may be clinically useful for protecting beta-cells against oxidative stress. Baraka Oil effectually reduced the FBS level in 72.7 % patients whose blood sugar level was above the normal limit. The drug does not show remarkable effect in fifteen patients, may be due to the cause of the psychosomatic status (biological variability) which is caused to the disease¹⁵. Elimandi A et al¹⁶ studied the effect of a 4-week intragastric gavage with a petroleum ether extract of *Nigella sativa* seeds on blood glucose, insulin and lipids in the normal rat. Petroleum ether extract caused a 25% reduction in food intake that translated into a transient weight loss. No sign of toxicity of the plant could be seen in vivo or in vitro. Fasting plasma glucose remained stable throughout *Nigella sativa* treatment. At the end of the 4-week treatment, *Nigella sativa*-treated rats had lower fasting plasma levels of insulin and triglycerides, and higher HDL-cholesterol as compared to pair-fed controls. Response to insulin was evaluated in hepatocytes isolated from animals of all groups by Western blot analysis of phosphorylated MAPK p44/42erk and PKB.

In vivo *Nigella sativa* treatment resulted in greater dose-dependent activation of MAPK and PKB in response to insulin. These results suggest that the petroleum ether extract of *Nigella sativa* has a slight anorexic effect, and that it contains the hypolipidemic activity previously obtained with the plant. More significantly, they demonstrated that in vivo treatment with the petroleum ether extract exerts an insulin-sensitizing action by enhancing the activity of the two major intracellular signal transduction pathways of the hormone's receptor. Antidiabetic properties of *N. sativa* seeds may be, at least partly, mediated by stimulated insulin release, and that the basic sub fraction largely contributes to this stimulatory effect. Further photochemical studies are underway in order to isolate the pharmacological compound(s) responsible for the insulinotropic effect of *N. sativa* seeds¹⁷.

Glycated hemoglobin HbA_{1c} is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement. In the normal 120-day lifespan of the red blood cell, glucose molecules react with hemoglobin, forming glycated hemoglobin. In individuals with poorly controlled diabetes, the quantities of these glycated hemoglobins are much higher than in healthy people. The International Diabetes Federation and American College of Endocrinology recommend HbA_{1c} values below 48 mmol/mol (6.5%), while American Diabetes Association recommends that the HbA_{1c} be below 53 mmol/mol (7.0%) for most patients¹⁸. HbA_{1c}

reflects average plasma glucose over the previous eight to 12 weeks¹⁹. It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes.

Reduction in LDL cholesterol was more (P value < 0.001) in *Nigella sativa* group (NS) as compared to standard group. Our results were the same as reported previously in various studies. Insulin resistance leads to the overproduction of very low density lipoproteins (VLDLs) and to reduced lipoprotein lipase activity, thereby resulting in dyslipidemia. Therefore, attainment of better glycaemic control may improve the lipid profile. Previous research workers²⁰ also reported the cholesterol lowering effect of *Nigella sativa* oil in animal studies. The presence of various unsaturated fatty acids like Arachidonic, eicosadienoic, linoleic, linolenic, oleic and almitoleic acid¹⁶ may be responsible for the improvement of lipid profile. The various mechanisms were proposed for the lowering of cholesterol. The seeds may either inhibit de novo cholesterol synthesis or stimulate bile acid excretion. It is well-known that both effects would lead to a decrease in serum cholesterol²¹. Further research is necessary to identify the mode of action of black cumin seeds.

Increase in High density lipoprotein (HDL) was more (P value > 0.05) in *Nigella sativa* group as compared to standard group. The same result was also reported previously in rats²². Reduction in Low density lipoprotein (LDL) cholesterol was significantly more (P value < 0.05) in *Nigella sativa* group as compared to standard group. LDL-c level may be decreased by increasing the production of LDL-c receptors²⁴. Improvement in triglyceride (TG) was more in standard as compared to NS group (P value < 0.001). The same results were reported previously¹⁴. Treatment of the dyslipidemia of metabolic syndrome should involve nonpharmacologic interventions, including weight loss, exercise, and a low-fat diet. Reducing LDL-C levels with use of 3-hydroxy-3-methylglutaryl I coenzyme A reductase inhibitors ("statins") is also appropriate for patients with metabolic syndrome. The ATP III guidelines recommend that LDL-C be the primary target of lipid-lowering therapy when a patient's triglyceride level is below 500 mg/dL. We had take atorvastatin because of certain advantages. Statins are competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG Co A) reductase, which catalyzes an early, rate limiting step in cholesterol biosynthesis. The statins are the most effective and best tolerated agents for treating dyslipidemia²⁵. Statins have certain other cardioprotective benefits besides LDL lowering like improvement in endothelial function²⁶, plaque stabilization²⁷ decreased the risk of coronary heart disease and levels of C-reactive proteins²⁸ inhibiting lipoprotein oxidation both in vivo and ex vivo²⁹ reduce platelet aggregation. Atorvastatin as a single agent may obviate the need for multiple drug therapy in high-risk patients³⁰. Atorvastatin is relatively more potent, cost effective and got the highest LDL cholesterol lowering efficacy at maximal daily dose of 80 mg. Hepatic cholesterol synthesis is maximal between midnight and 2:00 A.M. Thus statins with half life of 4 hours or less (all but atorvastatin and rosuvastatin) should be taken in the evening or bed time. Atorvastatin has a long half life (18-24 hours), which allows administration of this statin at any time of the day.

In our study we advised low dose aspirin to the patients of both standard and *Nigella sativa* group. People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. These abnormalities, however, are not routinely detected in clinical practice. A prothrombotic state, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected. The methanol soluble portion of black cumin oil showed inhibitory effects on Arachidonic acid induced platelet aggregation and blood coagulation. The methanol soluble part was further purified to isolate 2-(2-methoxypropyl)-5-methyl-1, 4-benzenediol, thymol and carvacrol, all having strong inhibitory

activity. These isolated compounds and related compounds were examined by the screening test for Arachidonic acid induced platelet aggregation and it was found that the compounds possessing aromatic hydroxyl and acetoxyl group had more potent activity than aspirin¹¹. An alternative approach to the prothrombotic state is antiplatelet therapy. For example, low-dose aspirin reduces CVD events in both secondary and primary prevention. Thus, use of aspirin for primary prevention in patients with metabolic syndrome is promising. According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio when 10-year risk for CHD is 10%. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established atherosclerotic cardiovascular disease (ASCVD) provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is an attractive therapeutic option to lower vascular events³¹.

CONCLUSION

Nigella sativa can be used as add on drug therapy in patients of metabolic syndrome with poor glycemic control. *Nigella sativa* is safe and an effective remedy in patients of metabolic syndrome. The most important action of *Nigella sativa* that may be responsible for its beneficial effect in metabolic syndrome is its insulin sensitizing action. The various components of *Nigella sativa* that may be responsible for its beneficial effects in insulin resistance syndrome are thymoquinone, thymol, various unsaturated fatty acids, lipase and tannins.

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