Effect of Kalonji (N. Sativa) Seeds on Glycemic Control of Patients with Type-2 Diabetes

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Abstract

The effects of Kalonji (Nigella sativa) on glycemic control and management of newly diagnosed diabetic-2patients was evaluated in this study. The effect of N. Sativa on glycated hemoglobin (HbA1c), fasting blood sugar (FBS), postprandial blood Sugar (PPBS) was examined. Material & Methods: One hundred patients were randomly divided into two groups (n=50 each). Group-1: patients were advised metformin 500 mg twice a day & atorvastatin 10 mg once a day for a period of eight weeks. Group-2: N. Sativa (NS) patients were advised recommended doses of N. Sativa (NS) in addition to the medication in group-1. Aspirin 150 mg was given in both group 1 & 2. Basal FBS, PPBS& HbA1c was measured at the beginning of the evaluation and once every 14 days during the study. Blood samples were collected before and after the intervention for lipid profile. Results: N. Sativa significantly lowered FBS, PPBS& HbA1c after 8 weeks. The NS group showed significant improvement regarding FBG, PPBG, HbA1c, and LDL-cholesterol. Conclusions: This study shows that it is appropriate to give N.Sativa to diabetes-2 patients with poor glycemic control along with the conventional medication. However, the physicians need to observe for any long-term changes and modify the dose.

Keywords*: Nigella sativa, Diabetes-2, glycemic control, Glycated hemoglobin (HbA1C)*

INTRODUCTION

Managing the glycemic control orlevels of blood sugar (glucose) in a person with diabetes mellitus has become a priority of medical care professionals in tackling diabetes effectively. Much evidence suggests that many of the long-term complications of diabetes, especially the microvascular complications, result from many years of hyperglycemia (elevated levels of glucose in the blood). Good glycemic control, in the sense of a "target" for treatment, has become an important goal of diabetes care. Generally, 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 and altered hypoglycemic control in diabetes-2 patients is under investigation by many laboratories worldwide. Alternative medicine has opened new door for the treatment of cardiometabolic disorders which has attained epidemic proportion throughout the world. The role of Nigella sativa also called kalonji in South Asia[1]or black cumin in Englishis believed to have beneficial role in diabetes and metabolic syndrome. Nigella sativa seed, used for centuries for medicinal and culinary purposes possess several pharmacological properties, including antioxidant [2], anti-inflammatory [3] hypoglycemic[4]antihypertensive [5, 6] and antihyperlipidemic [6] properties. In this study the effect of Nigella sativa on glycemic control of patients with diabetes-2 have been studied.

MATERIAL AND METHODS

The present study was conducted on diabetic patients with poor glycemic control (HbA1C >7 %) at Kannur Medical College Super specialty hospital. The study group comprised of 100diabetic patients 50 males and 50 females. The age group of the patients varied from 40 years to 60. 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. We had taken patients with diabetic-2 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. Patients were randomly divided into two groups. In group-1, patients were advised metformin 500 mg twice a day and atorvastatin 10 mg once a day for a period of eight weeks. In group -2 (N. sativa group) patients were given 2grams of Nigella sativa as add on therapy to

consumed after mid-day meal in addition to the medication of group-1. Aspirin 150 mg once a day was given in both groups.

N. Sativa Seeds

N. sativa seeds were procured locally. N.Sativa or kalonji, is well known in this region as N. Sativa is widely used in the Kerala's herbal industry. Seeds were washed, dried. After collecting base line data of glycemic control and lipid profile, a dose of two-month Nigella sativa seeds (2g/day) was given to patients in group-2 to be chewed and consumed. Each subject's glycemic control was measured by recording FBS, PPBS& HbA1c at the beginning of the trial, then once every two weeks during the trial. Blood samples were collected from each patient before and after the trial. Blood samples were assayed for serum lipid profiles. Advice about dietary and lifestyle changes were given to both Nigella sativa and standard groups. This study was approved by the ethical committee of Kannur Medical College. 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 HbA1c EDTA blood was used. HbA1c was assessed by enzymatic method. Fasting plasma glucose was measured by the hexokinase method.

STATISTICAL ANALYSIS

Paired t test was applied to know the intragroup difference of each variable before and after intervention. Unpaired t test was applied to know about intergroup difference between both groups. 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

Fasting blood sugar, PPBS, HbA1C, and LDL were significantly reduced (P value < 0.001) in group-2, as compared to group-1. Both intergroup and intragroup reduction in TG was significantly more (P value < 0.001) in group-1 as compared to group-2. HDL was increased in both group-1 and group-2 but neither intragroup nor intergroup difference werestatistically significant (P value 0.122). No adverse effects were reported by participants during the study and all subjects continued with the trial till the end of the study. Table-1 shows mean ± SD of different parameters before and after intervention in both groups. Table-2, shows postintervention mean ± SD of both groups. The LDL-cholesterol showed a marked reduction in the N. sativa group in the post intervent

Table 1:Parameters of Glucose and Lipid Metabolism Before and After the Intervention

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

**Data are mean ± SD, †Significantly different from baseline (P < 0·001).*

Group-1: (Std group): patients were advised metformin 500 mg twice a day and atorvastatin 10 mg once a day for a period of eight weeks. Group -2 (NS group:) patients were given 2grams of Nigella sativa as add on therapy in addition to std. group treatment

DISCUSSION

Nigella Sativa significantly decreased FBS, PPBS, HbA1C as compared to standard group. Significant decrease in HbA1c levels by Nigella sativa suggests that it can be used as an add on therapy in patients whose glycemic control cannot be achieved by conventional medication. Drugs like sulfonylurea are combined with insulin sensitizers like metformin or thiazolidinedione to manage glycemic control. Although new drugs are available, sulfonylureas still play a primary role in pharmacologic management of type 2 diabetes. Patients who respond best to treatment

with sulfonylureas include those with 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. Use of Metformin is based on the reason that it is a biguanide agent that lowers blood glucose primarily by decreasing hepatic glucose output and reducing insulin resistance. 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 mellitus [7].

Table 2: Parameters of Glucose and Lipid Metabolism Post Intervention In standard Group-1 and N. Sativa Group-2

Parameter	Mean ± SD Standard Group-1	Mean ± SD N. sativa Group-2
FBS‡	135.6951 ± 11.6414	144.3411 ± 12.9111
PPBS‡	198.0886 ± 17.5751	199.3902 ± 27.3605
HbA1C‡	7.18 ± 0.70	6.99 ± 0.83
TG	155.0122 ± 16.9724	150.3924 ± 38.9172
HDL	45.6829 ± 7.9378	46.6203 ± 6.4456
LDL‡	128.2405 ±12.5820	117.8780 ± 20.4107

Data are mean ± SD.

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

Group-1: (Std group): patients were advised metformin 500 mg twice a day and atorvastatin 10 mg once a day for a period of eight weeks. Group -2 (NS group:) patients were given 2 grams of Nigella sativa as add on therapy in addition to std. group treatment

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 glucose [8]. Various mechanisms have been proposed for hypoglycemic activity of Nigella sativa were insulin sensitizing action [9] and stimulatory effect on beta cell function 8. In view of the folkloric use of plant mixture extracts for treatment of diabetes in the Middle East, Al-Awadi and Gumaa [10] studied a plant mixture (Nigella sativa, Myrrh, Gum olybanum 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 significantly [9]. Administration of volatile oil of N. sativa seeds produced a significant hypoglycemic effect in normal and alloxan-induced diabetic rabbits [10]. 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. It was obvious 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 2 diabetes model [11, 12] 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 al [13] studied the, effect of N. Sativa seed oil on blood glucose concentrations in Streptozotocin-induced diabetic rats. The effect of N. Sativa 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 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 hypoglycemic [13]. Kanter M et al [14] studied the possible protective effects of Nigella Sativa L. (NS) against beta-cell damage from streptozotocin (STZ)-induced diabetes in rats. They found that N. Sativa treatment exerts a therapeutic protective effect in diabetes by decreasing oxidative stress and preserving pancreatic beta-cell integrity. Consequently, N. Sativa 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 disease [15]. Elimandi et al [16] studied the effect of a 4-week intragastrical 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 HDLcholesterol as compared to pair-fed controls. Antidiabetic properties of N. sativa seeds may be, at least partly, mediated by stimulated insulin release. Photochemical studies are underway to isolate the pharmacological compound(s) responsible for the insulinotropic effect of N. sativa seeds [17] Glycated hemoglobin HbA1c 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 nonenzymic 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 HbA1c values below 48 mmol/mol (6.5%), while American Diabetes Association recommends that the HbA1c be below 53 mmol/mol (7.0%) for most patients [18]. HbA1c reflects average plasma glucose over the previous eight to 12 weeks [19]. 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 glycemic 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 in Nigella sativa group 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 glycemic control may improve the lipid profile. Previous research workers [20] also reported the cholesterol lowering effect of Nigella sativa oil in animal studies. The various mechanisms were proposed for the lowering of cholesterol. The seeds may inhibit de novo cholesterol synthesis or stimulate bile acid excretion. It is well known that both effects would lead to a decrease in serum cholesterol [21]. Further research is necessary to identify the mechanism of action of N. Sativa seeds. Increase in High density lipoprotein (HDL) was more in Nigella sativa group as compared to standard group. The same result was also reported previously in rats [22, 23] Reduction in Low density lipoprotein (LDL) cholesterol was significantly more in Nigella sativa group as compared to standard group. LDL-c level may be decreased by increasing the production of LDL-c receptors [24-27]. Improvement in triglyceride (TG) was more in standard as compared to N. Sativa group (P value < 0.001).

CONCLUSION

Nigella sativa can be used as add on drug therapy in patients of metabolic syndrome with poor glycemic control. Nigella sativa is safe andan 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. N. Sativa has the potential to be used as a natural adjuvant to oral glucose lowering drugs in the management of type 2 diabetes mellitus. As NS is a very low cost herb, therefore the potential cost benefit ratio will be in favor of benefit. Further clinical trials are recommended to move forward in this promising area of research.

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