Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20160748

Research Article

To study the efficacy and tolerability of fenugreek seed powder as add-on therapy with metformin in patients of type-2 diabetes mellitus

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Received: 23 December 2015
Accepted: 03 February 2016

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ABSTRACT

Background: Fenugreek, an ancient herb has been known for its culinary and medicinal value in Indian Subcontinent. Its seeds, rich in fibers and phytochemical compounds, have been investigated for their hypoglycemic and multiple benefits. This study was thus undertaken to assess the anti-hyperglycemic effect of fenugreek seeds in patients of Type 2 Diabetes Mellitus (DM) as add-on therapy with metformin.
Methods: An open-labelled comparative study of 12 weeks duration was conducted on patients (randomly divided in 2 groups of 30 each) of Type 2 DM. Group 1 was given metformin 500 mg twice a day while group 2 was given 500 mg of metformin along with fenugreek seed powder capsule,1 gm thrice a day. Weekly evaluation for fasting and post-prandial blood sugar was done. HbA1c estimation was done at the beginning and at the end of the study. Student's t-test (paired and unpaired) was applied for statistical analysis.
Results: After 12 weeks of treatment, there was significant fall in fasting, as well as postprandial blood sugar and HbA1c levels in group 1 and group 2. However this improvement was statistically more significant in group 2 when compared to group 1.
Conclusions: This study shows the beneficial effects of fenugreek seeds on glycemic profile in patients of Type 2 DM and can be used as an add-on therapy with metformin in management of Type 2 DM.

Keywords: Type 2 Diabetes Mellitus (DM), Fenugreek

INTRODUCTION

Diabetes Mellitus (DM) refers to group of common metabolic disorders that share the common phenotype of hyperglycaemia. The different types of DM are caused by the complex interplay of genetic and environmental factors. The factors that lead to hyperglycaemia are decrease insulin secretion, reduced glucose utilization and increased glucose production.[1] Symptoms of hyperglycaemia include polyuria, polydipsia, weight loss, sometimes weight loss with polyphagia and blurred vision.

The risk of developing Diabetes Mellitus increases with increasing age, lack of physical activity, obesity, individuals with hypertension, dyslipidemia, women with prior gestational Diabetes Mellitus and with certain racial and ethnic groups having a strong genetic predisposition. Diabetes Mellitus is classified on the basis of the pathogenic process that leads to hyperglycaemia .The two broad categories of DM are Type 1 and Type 2. Both of these types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic process. The other categories that have been evolved are on the basis of aetiology. e. g. gestational diabetes, drug induced diabetes and hyperglycaemia associated with a myriad number of reasons.[2]

Type-1 Diabetes Mellitus (immune mediated diabetes or insulin-dependent diabetes or juvenile onset diabetes) is the result of a cell- mediated auto-immune destruction of β-cells in the pancreas. Type-2 Diabetes Mellitus (Non-insulin-dependent Diabetes or Adult-onset Diabetes) constitutes about 90-95% of all the reported cases of Diabetes. It encompasses individuals who have insulin resistance and relative (rather than absolute) insulin deficiency.[3] There could be a predominantly insulin secretory defect with insulin. Type-2 Diabetes Mellitus is at present one of the most challenging health care problems, which require optimum management. The treatment of Type-2 Diabetes Mellitus aims at providing structured education to the patients with Type-2 Diabetes Mellitus and to improve the overall quality of life by providing psychological and pharmacological support.[4]

An HbA1c target of 7% among the people with Type-2 Diabetes mellitus is reasonable to reduce the risk of micro-vascular and macro-vascular complications.[5] The treatment of the patients with type 2 DM should include diet, life style modifications (exercise, smoking cessation), good glycemic control with medical nutrition therapy.[1]

Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose lowering agent. Its development was based on the use of Galega officinalis to treat Type 2 DM.[6]

Presently metformin has been incorporated in the early stage of management of Type 2 DM as the first choice oral agent, along with appropriate diet control and lifestyle advice.[7] Alternate therapies with anti-diabetic activity have also been researched relatively extensively in India. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated for the treatment of Diabetes.[6]

Fenugreek (Trigonella foenum graceum) is one of the oldest herb used for medicinal purposes in India and its history dates back to Egyptian civilization.[8] Fenugreek seeds contain alkaloids, including trigonelline, gentianine and carpaine compounds. These seeds are a rich source of fiber and protein. The fiber may be further classed as gum (gel fiber) and neutral detergent fiber.[1,6,8] The seeds also contain fibre-galcatomannan, 4-hydroxyisoleucine- a novel amino acid and fenugreekine, a component that may have hypoglycemic activity.[9] Lignin, another form of crude fiber, is not a carbohydrate per se, but it is of plant origin and is also indigestible, which prevents the rapid uptake of glucose in the small intestine, slows gastric emptying, aids in blood sugar retention in diabetic patients and may also be effective in the treatment of hypercholesterolemia.[10]

Broca et al reported that the hypoglycemic action of fenugreek seeds is exerted through 4- hydroxyleucine which stimulates insulin secretion. Thus acting as a secretagogue.[11]

Thus the present study was designed to study the efficacy of fenugreek seed powder used as add-on therapy with metformin in patients of Type-2 Diabetes mellitus and to compare the variations in blood glucose levels with fenugreek seed powder and metformin combination versus metformin alone in patients of Type-2 Diabetes mellitus. And additionally to study the safety and tolerability of fenugreek seed powder along with metformin in patients of Type-2 Diabetes mellitus.

METHODS

This twelve week long, open, standard controlled and parallel randomized study involved 60 patients, of either sex, with Type 2 DM, fulfilling the inclusion criteria and attending the Medicine OPD at Sri Guru Ram Das Charitable Hospital attached to Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar. The patients were randomly distributed into two groups, i.e. Group 1 and Group 2 consisting of thirty patients each. Written Informed Consent was taken from the patients to be included in the present study and all the risks and the benefits were explained to each patient in their own language. Patients were advised to undertake diet control and regular exercise as per the protocol designed by W.H.O.

Inclusion criteria

Newly diagnosed Type-2 Diabetes Mellitus (Type 2 DM) patients of either sex, aged 30-70 years, having Fasting Blood Glucose > 126 mg/dl were included in the study.

Exclusion criteria

1. Patients with Type-1 Diabetes Mellitus.
2. Patients with history of ketoacidosis in the past.
3. Patient with a history of hypersensitivity to fenugreek seed powder.
4. Patient with a history of bleeding disorders.
5. Patient with a history of surgery in the past six weeks.
6. Pregnant females.
7. Patient with a history of drug abuse and steroid treatment.

Intervention

Patients in Group 1 were given only Metformin 500 mg twice a day after meals for 12 weeks. Patients in Group 2 were given fenugreek seed powder capsules in a dose of 1 capsule of 1 gm each thrice a day before meals along with Metformin 500 mg twice a day after meals for 12 weeks.

The patients were investigated for FBG and PPBG every week for twelve weeks. While HbA1c estimation was

done at the beginning of the study and at the end of the study.

The patients were advised to report immediately in case they developed any adverse reaction e.g. nausea, vomiting, abdominal pain, muscle ache, fever, weight gain, diarrhoea, flatulence or any other type of side effect.

Statistical Analysis

Statistical analysis was done using Student's paired and unpaired 't' test. Paired 't' test was done to determine the significance within the groups and unpaired 't' test was done to determine the significance between the groups. The results of the study are depicted in the tables and the graphs. The level of significance was determined as its 'p' value with $p > 0.05$ taken as not significant, $p < 0.05$ taken as significant at 5% significance level, $p < 0.01$ taken as significant at 1% significance level & $p < 0.001$ taken as highly significant.

RESULTS

In this study 60 (36 males and 24 females) patients were randomly distributed in 2 groups by a computer generated series. The mean age of the patients at the time of visit in Group 1 is 53.23±8.19 years and in Group 2 was 52.97±8.00 years which was statistically not significant. There was not much difference in the baseline Body Mass Index (BMI) of both the groups with the patients in the Group 1 having a BMI of 25.91±1.92 and the patients in Group 2 having a BMI 25.17 ± 2.88 indicating that majority of the patients were overweight. There was not much fluctuation in the BMI at the end of study (Table 1).

Table 1: Anthropometric comparison of group 1 and group 2.

	Group 1 (n=30)			Group 2 (n=30)		
	Day 0	12^{TH} Week	P value	Day 0	12^{TH} Week	P value
Weight (kg)	70.4±11.53	69.33±11.42	ns	69.9±12.77	68.05±12.51	ns
Height(cm)	164.23 ± 8.36	------	ns	166±8.67	------	ns
BMI (kg/m²)	25.91±1.92	25.51±1.91	ns	25.17 ± 2.88	24.49±2.74	ns

Table 2 : Fasting blood glucose levels (Mean±SD) on day zero, 1st, 2nd, 3rd, 4th, 5th, 6th,7th, 8th, 9th, 10th, 11th, 12th week in group 1 and group 2.

Duration	Group 1(n=30)		Group 2 (n=30)	
	Mean ± SD	Change from baseline	Mean ± SD	Change from baseline
Day 0	162.0667±11.17	----------	164.1333± 17.79	--------
1^{st} week	158.56±11.11	$3.5±1.52^{HS}$	162.267±24.26	$1.86±11.78^{NS}$
2^{nd} week	156..53±10.77	$5.53±2.14^{HS}$	155.166±15.91	$8.96667±9.90^{HS}$
3^{rd} week	154.56±10.64	$7.50±1.96^{HS}$	152.46±14.48	$11.66667±8.99^{HS}$
4^{th} week	152.20±10.68	$9.86±2.73^{HS}$	151.83±16.06	$12.30±10.67^{HS}$
5^{th} week	150.60±10.23	$11.46±2.96^{HS}$	148.80±16.81	$15.333±9.7^{HS}$
6^{th} week	148.60±10.20	$13.46±2.64^{HS}$	145.26±16.44	$18.866±10.20^{HS}$
7^{th} week	146.4333±10.04	$15.63±2.73^{HS}$	144.10±12.89	$20.033±11.77^{HS}$
8^{th} week	144.43±9.86	$17.63±3.20^{HS}$	141.23±10.11	$22.900±13.22^{HS}$
9^{th} week	142.40±9.8	$19.66±3.07^{HS}$	137.36±11.00	$26.766±11.37^{HS}$
10^{th} week	140.30±9.8	$21.76±3.71^{HS}$	133.83±9.3	$30.30±14.02^{HS}$
11^{th} week	138.26±9.8	$23.80±3.77^{HS}$	130.30±10.12	$33.83±14.02^{HS}$
12^{th} week	136.23±9.18	$25.83±4.18^{HS}$	126.8333	$37.30±14.74^{HS}$

Fasting Blood Glucose FBG) levels were measured at the beginning of the study and then weekly till the end of 12 weeks. There was a significant reduction in mean FBG levels of both the groups. However, the reduction in mean FBG level in Group 2 was greater than in Group 1 ($p<0.001$). An analysis of the mean percentage in FBG levels of both group at the end of 12 weeks revealed greater reduction in group 1. ($p<0.001$) (Figure 1, Table 2).

Mean Baseline Post Prandial Blood Glucose (PPBG) levels was greater in Group 1 (222.73±12.44 mg/dl) as compared to Group 2 (213.56± 23.21 mg/dl). However there was a greater reduction in PPBG levels in Group 2 as compared to Group 1. Furthermore mean percentage change was greater in Group 2 than in Group 1 ($p<0.001$) (Figure 2, Table 3).

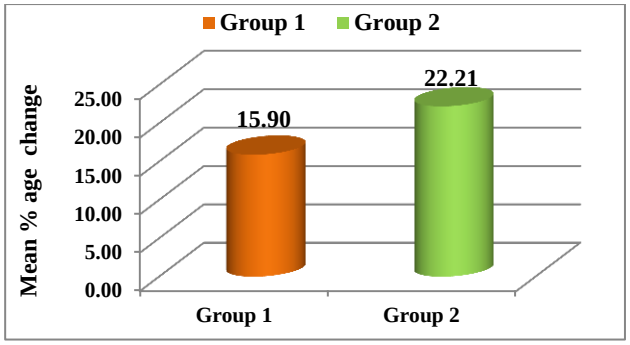

Figure 1: Mean percentage change in fasting blood glucose in group 1 and group 2 (p<0.001 in both the groups).

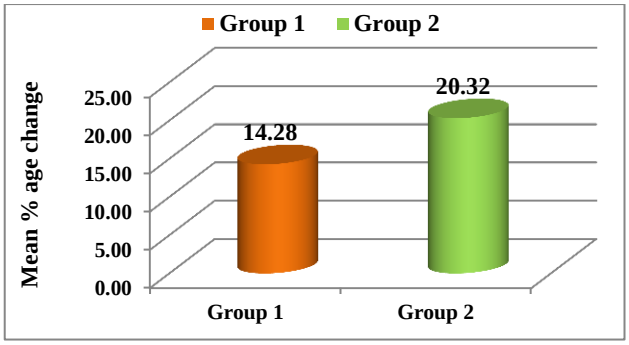

Figure 2: Mean percentage change in post prandial blood glucose in group 1 and 2 (p<0.001 in both the groups).

Table 3: Post prandial blood glucose levels (Mean±SD) on day zero, 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th week in group 1 and group.

Duration	Group1(n=30)		Group2 (n=30)	
	Mean ± SD	Change from baseline	Mean ± SD	Change from baseline
Day 0	222.73±12.44	……..	213.56±23.21	…….
1st week	219.86±11.7	2.86±2.02^{HS}	207.1±21.85	6.44±4.10^{HS}
2nd week	217.33±11.77	5.4±2.11^{HS}	204.66±17.84	8.9±14.82^{S}
3rd week	214.33±12.06	8.4±2.017^{HS}	198.20±16.63	15.3±11.38^{HS}
4th week	211.50±11.96	11.23±2.96^{HS}	194.7±15.4	18.86±12.67^{HS}
5th week	209.33±12.12	13.4±3.00^{HS}	192.16±15.83	21.40±16.12^{HS}
6th week	205.73±11.91	17.00±2.80^{HS}	185.96±19.7	30.16±18.4^{HS}
7th week	203.56±11.7	19.16±2.9^{HS}	183.4017.9	30.46±18.9^{HS}
8th week	200.266±11.7	22.46±2.75^{HS}	183.1±12.26	34.96±17.8^{HS}
9th week	198.36±12.52	24.36±3.17^{HS}	178.60±12.20	37.26±18.89^{HS}
10th week	195.32±11.96	27.40±3.31^{HS}	176.30±12.04	37.26±18.89^{HS}
11th week	193.00±11.96	29.73±3.0^{HS}	173.63±10.53	39.93±19.10^{HS}
12th week	191.00±12.69	31.73±2.76^{HS}	169.03±12.62	44.53±18.7^{HS}

Group 2 showed a greater reduction in HbA1c levels as compared to Group 1 at the end of 12 weeks of study. However there was a highly significant reduction in HbA1c levels in both the groups (p<0.001) (Figure 3).

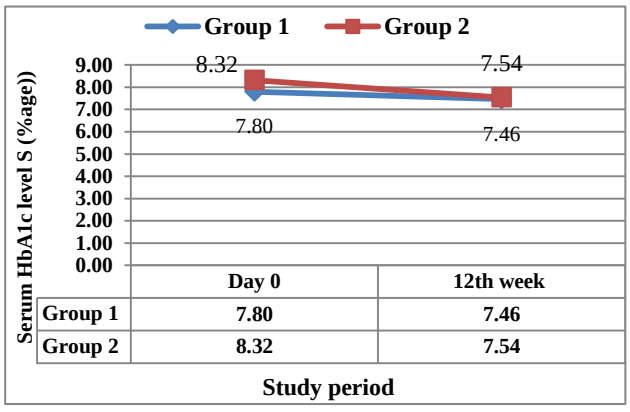

Figure 3: Serum hba1c levels on day 0 and 12th week in group 1 and group 2.

Table 4: Incidence of adverse effects in group 1 and group 2.

Adverse effect	Group 1 N (%)	Group 2 N (%)
Wheezing\ Rhinnorhea	0	0
diarrhoea	0	1 (3%)
Flatulence	0	1 (3%)
Nausea\ Vomiting	0	1 (3%)
Facial swelling	0	1 (3%)
Bleeding tendency	0	0
Fainting	0	0
Numbness	0	0
Hypoglycemia	0	0
Pallor	0	0
Tiredness/ Weakness	0	0
Any other (itching)	0	1 (3%)

No side effects were reported in Group 1. While in Group 2 diarrhoea, nausea/ vomiting, facial swelling, flatulence and itching each was reported in 3% of the patients. All

the adverse effects were mild in nature and none of the patients was withdrawn from the study (Table 4).

DISCUSSION

Type 2 DM is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.[1] Type 2 DM usually precipitates from the inability of the pancreatic beta cells to adapt to the reductions in insulin sensitivity that occur over a life time. The most common factors that place an increased burden on beta cells are puberty, overeating, sedentary life style, pregnancy leading to weight gain and hypertension. An underlying genetic predisposition also appears to be critical.[12,13]

The present study was conducted in this institute from September 2013– Sept 2015. In this study we compared the anti-hyperglycemic effect of fenugreek as an adjunct to metformin and metformin when used alone in the treatment of Type 2 DM patients. Sixty patients of Type 2 DM were included in the study and were divided in two groups of 30 each. Group 1 received metformin 500 mg twice daily after meals. Group 2 received metformin 500 mg twice daily after meals along with fenugreek seed powder in a dose of 1 capsule thrice a day (1 capsule containing 1 gm). The patients in each group received the treatment for 12 weeks duration.

There was a significant decline ($p<0.05$) in the mean FBG in Group 1 patients. Similarly there was a highly significant reduction ($p<0.001$) in FBG in Group 2 patients. However the reduction in Group 2 was greater than in Group 1. Similarly there was a highly significant ($p<0.001$) reduction in PPBG in both the groups. This is supported by studies conducted by Bordia et al.[14] However the reduction in PPBG was greater in Group 2. Besides this, there was a highly significant reduction in HbA1c levels in both the groups ($p<0.001$). However the mean decrease in HbA1c was greater in Group 2 as compared to Group 1. The results of the present study are supported by a randomized control trial conducted by Ansari, et al in which fenugreek seed powder was administered as an add- on therapy to Type 2 DM patients for a duration of three months resulted in significant reduction in HbA1c levels ($p<0.001$).

Similar findings were present in the study conducted by Lu et al where fenugreek seed powder was used as add-on therapy along with anti-hyperglycaemic agents in Type 2 DM patients for 12 weeks duration. At the end of 12 weeks the treated group in which fenugreek seed powder was used as an add-on therapy to the anti-hyperglycaemic agent showed statistically decrease in FBG, 2h PPBG, HbA1c as compared to those in the control group who received only anti-hyperglycaemic agent ($p< 0.05$).[15]

A landmark study was conducted by Gupta et al in 2001 to evaluate the effect of fenugreek seed on the glycemic control and insulin resistance in Type 2 DM patients for a period of two months. For that study 1 gm/day hydroalcoholic extract of fenugreek was taken. There was a significant improvement in the FBG and PPBG.. These findings are very much supportive to those in the present study where there was significant improvement in glycemic profile of the patient.[16]

The mechanism of hypoglycemic effect of fenugreek seeds in Diabetes is usually associated with the insulin signalling pathway. The fenugreek seed activate the insulin receptors and its downstream signalling molecules in adipocytes and liver cells. In an experiment conducted by Vijayakumara et al alloxan was given intraperitoneally to albino mice.[17] The active principle responsible for anti-hyperglycemic activity is largely due to fenugreeks saponins, high fibre content, the amino acid hydroxyisoleucine and the major alkaloid trigonelline. Anti-hyperglycemic effect was due to stimulation of insulin secretion and delayed gastric emptying caused by high fibre content, inhibiting carbohydrate enzymes. This is further supported by various studies by Ramesh Babu et al, Muraki et al, Puri, et al.[18-20] Hydroxyleucine fraction is also responsible for anti-hyperglycemic action by non-insulin dependent pathway as demonstrated by Haeri, et al and is a potent secretor of insulin secretion as stated by Sauvaire, et al.[21,22] The active subfraction is contained in the testa and endosperm of fenugreek as was confirmed by the animal studies conducted by Ribes, et al.[23]

As far as our study was concerned no major side effects were reported in Group 1.While in Group 2 one case each of nausea/vomiting, diarrhoea, facial swelling, bleeding tendency and itching were reported, which were mild in nature**.**

Neelakantan, et al conducted a meta- analysis and reported the adverse effects that occurred with the use of fenugreek seed powder in Type 2 DM patients. In one study conducted by Chevassus one mild case of abdominal symptoms was reported.[11] As already mentioned the study conducted by Gupta et al on 12 patients, 5 patients developed dyspepsia and mild abdominal symptoms.[16] Lu et al reported that of the 46 patients in the treatment group, two developed abdominal discomfort and nausea and one patient developed diarrhoea. The symptoms disappeared once the drug was withdrawn for 2 days. Again after resuming the treatment, no adverse reaction appeared and all patients completed the trial.[15]

CONCLUSION

The present study demonstrated that fenugreek seed powder when used as add-on therapy with metformin in Type 2 DM has a significant effect on glycemic profile. Thus we conclude that fenugreek seed powder may be a promising additional therapy for the management of Type 2 DM as these are widely available at low cost in third world countries like India.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kaur M, Singh N, Sharma G, Singh D. To study the efficacy and tolerability of fenugreek seed powder as add-on therapy with metformin in patients of type-2 diabetes mellitus. Int J Basic Clin Pharmacol 2016;5:378-83.