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Antidiabetic and hypolipidemic effects of fenugreek in Prediabetic subjects with dietary modifications

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Abstract---Objectives: The incidence of Diabetes Mellitus in India is growing day by day. Hyperlipidemia is also a major cause of health

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complication. Trigonella-foenum-graecum is one of the medicinal plants used in the management of Diabetes and Hyperlipidemia. The present study was conducted to assess the effect of fenugreek and dietery modification on HbA1c and on lipid profile. Materials and Methods: A Total of 280 prediabetics were included in the study. Patients were randomized and one group of patients receive 10 gm of fenugreek powder in hot water every day, while the second group did not receive. The parameters were assessed on the first visit and every 3months for 12 months. Results: HbA1c and Lipid profiles were analyzed, Dietary addition of fenugreek cause reduction in blood glucose and cholesterol levels. Conclusion: Conclusion: The present study showed that the administration of Trigonella-foenum-graecum seed powder had pronounced effects in improving lipid profile and prevents the T2DM progression from prediabetes with no adverse effects. Therefore, Fenugreek improved the lipid profile and act as a hypocholesterolemic by reducing the LDLc levels. Dietary addition of fenugreek can have a synergistic effect along with diet control on HbA1c and lipid profile.

Keywords---glycosylated haemoglobin/HbA1c, prediabetics, fenugreek, diet modification, lipid profile, TG, HDL, LDL, VLDL.

Introduction

Diabetes mellitus is a metabolic disorder in which individuals has abnormal high level blood glucose levels either due to insulin production inadequate from pancreatic cells or resistance to body's cells to insulin or both[1]. The American Diabetes Association (ADA) includes hemoglobin A1c between 5.7 and 6.4 per cent in addition to OGTT of 140-199 mg/dl and FPG between 100 and 125 mg/dl considers Prediabetic[2] According to National Urban Diabetes Survey, the estimated prevalence of prediabetes in India is 14%[3]. according to India the Global Burden of Disease Study 1990-2016, the prevalence of diabetes mellitus in adults aged 20 years or older in India is 7.7%. Approximately 80% of diabetic people in low- and middle-income countries such as Asia and the eastern Pacific regions[4].

Currently in India, about 72.96 million people suffer from diabetes. The prevalence in urban areas is approximately about 10.9%-14.2% and in rural India it is about 3.0-7.8%. in the 21 century, this is one of the most serious public health problems. India is the country with the most diabetes patients after china[5]. The comprehensive overview of current and future prediabetes prevalence was published by International Diabetes Federation (IDF) with IGT reference aged between 20-79 years. Hyperlipidemia is considered one of the major risk factors causing cardiovascular diseases (CVDs). CVDs accounts for one third of total deaths around the world, it is believed that CVDs will turn out to be the main cause of death and disability worldwide by the year 2020[1]. Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very

low-density lipoprotein and low-density lipoprotein and reduced high-density lipoprotein levels[6].

Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD). There is a strong relation between IHD and the high mortality rate. Furthermore, elevated plasma cholesterol levels cause more than four million deaths in a year[2]. Atherosclerosis is a process of arteries hardening due to deposition of cholesterol in the arterial wall which causes narrowing of the arteries. Atherosclerosis and atherosclerosis-associated disorders like coronary, cerebrovascular and peripheral vascular diseases are accelerated by the presence of hyperlipidemia. Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases[2].

The herb fenugreek (*Trigonellafoenumgraecum* L., family: Fabaceae) is one of the older and most promising traditional medicinal plants cultivated widely in India, Egypt, and Middle Eastern countries[3]. From the decades, researchers from different disciplines were using the fenugreek as an investigation product to explore the therapeutic benefits against diabetes, hyperlipidemia, hepatotoxicity, inflammation, bacterial and fungal infections, neurotoxicity, cancer, ulcers, wound, weakness and edema of the legs[7]. The pharmacological effects of Fenugreek have wide range of active bioactive compounds such as steroids, polyphenols, alkaloids, lipids, hydrocarbons, saponins, flavonoids, carbohydrates, amino acids and galactomannan fibers[8]. In traditional medicine, uses of plant based agents are important to control the diabetes as per WHO recommendations. As compared to synthetic drugs, herbal preparations are less frequently produce side effects and considered to be less toxic to the humans[8]. The present study evaluated the antidiabetic and hypolipidemic properties of Fenugreek among Prediabetic participants, the ability of Fenugreek to reduce diabetic progression, controls hyperlipidaemic state at a tertiary care hospital.

Materials and Methods

This is a prospective, randomized, parallel open labeled single-center study was conducted in a tertiary care hospital. Patients were screened at general medicine outpatient department. Before recruiting participants blood samples were collected for screening of OGTT, Hb1Ac and lipid profile. Patients of hyperlipidaemia identified and were counseled and written informed consent was taken to participate in the study. Ethical committee approval was taken before study. A total of 280 patients were included in the study, patients were divided into two groups and 140 in each group. After obtaining written valid and informed consent, baseline demographic data were collected.

Inclusion criteria

Prediabetes was diagnosed with HbA1c levels between 5.7% and 6.4%. Patients were tested to have high abnormal lipid profile with age groups of 20-50 years of either sex were included. Inclusion criterion included subjects of familial history

and sedentary life style, Persons with BMI in between 25-29.9, Subjects like Obese, Patients who are willing to give written informed consent.

Exclusion criteria

Those who had a history of cancer or any major illness of the kidney and nervous system. Pregnant women, breast feeding or planning a pregnancy during the course of the study. Those who were having habit of smoking, chewing tobacco and alcohol. Familial histories such as congestive heart failure, renal failure, jaundice and genetic abnormalities. Patients who are not willing to give written informed consent to participate in the study.

Grouping and Posology

Patients were randomized to receive fenugreek seed powder 10gms along with water half an hour before meals along with their dietary modification. Patients were not blinded for this study and they were asked to follow the same dosage regimen up to the end of the study. Sample size calculated by the following formula,

$$n \geq \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

Primary endpoints: HbA1c, Lipid Level.

Primary outcome measures: Patients were serially followed up every 3rd month for 12 months. During each visit HbA1c, lipid profile were assessed.

Statistical analysis

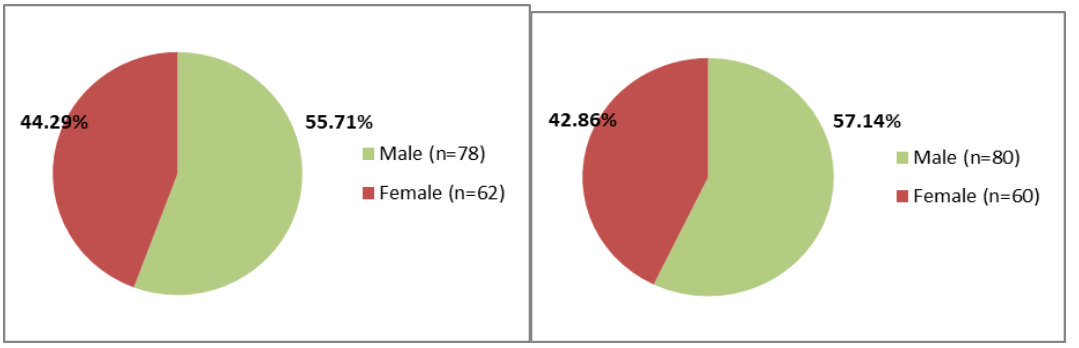
Baseline demographics are showed in mean, median, SD, proportions and IQR, Baseline values among study groups were analyzed by unpaired t-test, Incidence rate of diabetes during the study period among study groups were analyzed by chi-square test, Change in lipid profile among study groups were analyzed by unpaired t-test.

Results

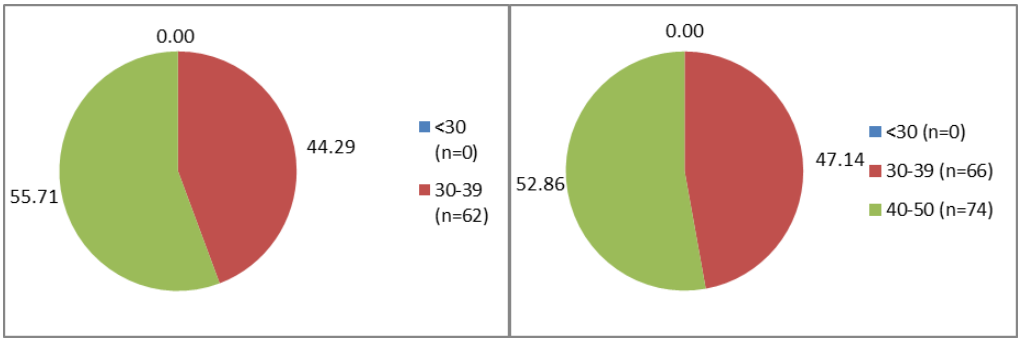
A total of 300 participants were recruited and 20 were excluded due to various reasons. A total of 280 participants completed entire study and their data was analyzed. There was no statistical difference in baseline demographics between study groups. Age between 32 and 50 years were recruited according to inclusion criteria. At baseline mean body mass index (BMI) was 27 kg/m^2 in both the study groups. Nearly 90% of study participants were reported as overweight at baseline in both the groups. Only 5-10% of study participants belong to high socioeconomic status and rest of them fell under either low or middle socioeconomic status. Sub-group analysis of age reveals that no patient was

observed under the age of 30 years in the both the groups. A total of 55.7% and 52.9% of study participants were in the age group of 40-50 years in dietary modification alone and dietary modification + Fenugreek group respectively. Detailed subgroup analysis showed in Figures.

Subgroup analysis of Gender among groups

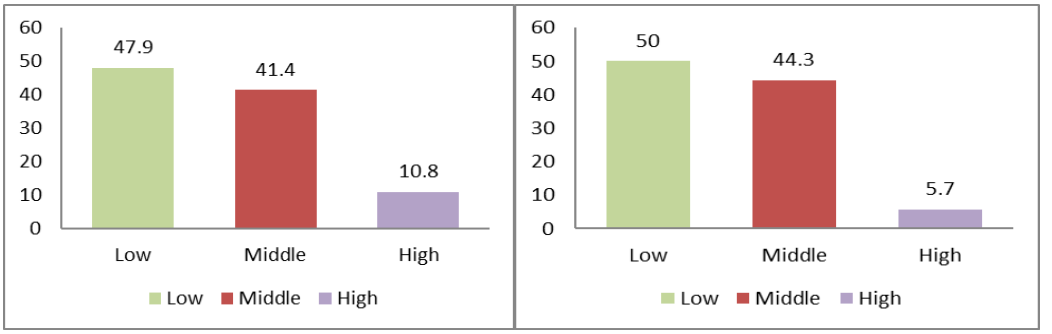


Subgroup analysis of Age among groups



Subgroup analysis of weight categories among groups

Subgroup analysis of Socioeconomic status among groups



Change in HbA1c levels among study groups at different points in time is shown in Table No 1. Both study and control groups had 5.7% of median HbA1c at baseline. Dietary modification + Fenugreek group showed significant fall in HbA1c level at 3, 6 and 12 months. The group with participants following diet modification alone showed exponentially increasing trend of HbA1c over the time.

Table 1
Change in HbA1c levels among study groups

Time (Months)	Group 1 (Dietary modification alone), HbA1c (%), Median (IQR) (n=140)	Group 2 (Dietary modification + Fenugreek) HbA1c (%), Median (IQR) (n=140)	P-Value
0	5.7 (5.4-5.9)	5.7 (5.3-5.9)	0.94
3	5.8 (5.6-6.0)	5.6 (5.4-5.8)	0.71
6	5.7 (5.4-6.0)	5.3 (5.0-5.5)	0.05
12	6 (5.8-6.2)	5 (4.8-5.2)	0.05

Cumulative incidence rates of diabetes mellitus among study groups were showed in Table no: 2. Dietary modification + Fenugreek group showed significantly lower curve compared to dietary modification alone group. All cumulative incidence rates at each time points showed significant difference among study groups in favour of dietary modification + Fenugreek group

Table 2
Cumulative incidence rate of diabetes mellitus at every study period for the length of 12 months among groups

Category	0 month	3rd month	6th month	12th month
Dietary modification alone				
T2DM (n=)	0	6	14	22
Cumulative incidence (%)	0	4.3	10.0	15.7
2h OGTT (mean±SD)	178.7±11.4	224.6±14.2	230.8±14.8	236.2±15.0

Dietary modification + Fenugreek				
T2DM (n=)	0	0	2	2
Cumulative incidence (%)	0	0	1.4	1.4
2h OGTT (mean±SD)	162.7±9.6	162.7±9.6	218.2±11.8	228.2±13.2

Table 3
Changes in lipid profile among dietary modification alone group

Category	Time intervals (Months)			
	0 (Baseline, (Mean±SD)	3 (Mean±SD)	6 (Mean±SD)	12 (Mean±SD)
TC, (mg/dl)	185.5±24.0	184.2±23.9 p =0.650	184.0±23.9 p =0.600	183.1±23.7 p =0.400
TG, (mg/dl)	164.4±28.1	164.1±28.0 p =0.928	163.8±27.9 p =0.857	162.2±27.8 p =0.510
HDLc, (mg/dl)	36.2±6.4	36.8±6.4 p =0.037	37.0±6.6 p =0.021	37.4±6.7 p =0.005
LDLc, (mg/dl)	117.0±18.2	116.2±18.1 p =0.712	115.6±17.9 p =0.516	115.2±17.9 p =0.404
VLDLc, (mg/dl)	30.2±5.8	30.1±5.7 p =0.884	30.0±5.6 p =0.769	29.8±5.4 p =0.550

*Compared with baseline values and p-value was calculated by using paired t-test

Table 4
Change in lipid profile among dietary modification + Fenugreek group

Category	Time intervals (Months)			
	0 (Baseline, (Mean±SD)	3 (Mean±SD)	6 (Mean±SD)	12 (Mean±SD)
TC, (mg/dl)	184.1±24.8	180.2±22.4 p=0.168	176.1±24.8 p =0.149	173.1±24.8 p =0.053
TGs, (mg/dl)	168.1±29.0	160.6±25.8 p =0.023	154.1±24.2 p =0.023	150.1±22.8 p =0.021
HDLc, (mg/dl)	37.9±7.2	40.9±7.8 p=0.019	42.1±7.9 p=0.010	44.0±8.0 p=0.001
LDLc, (mg/dl)	118.0±18.4	110.2±16.8 p =0.027	106.8±16.0 p =0.016	100.4±15.2 p =0.006
VLDLc, (mg/dl)	31.3±5.9	29.5±5.2 p =0.007	27.8±4.3 p =0.005	26.2±4.1 p =0.005
	# p =0.696	# p =0.1496	# p =0.0071	# p =0.006
	$ p =0.279	$ p =0.271	$ p =0.059	$ p =0.051
	& p =0.037	& p =0.021	& p =0.001	& p =0.001
	^ p =0.647	^ p =0.044	^ p =0.031	^ p =0.011
	! p =0.358	! p =0.2168	! p =0.069	! p =0.053

*compared with baseline values and p-value was calculated by using paired t-test; #comparison with Serum cholesterol values between groups and p-value was calculated by using unpaired t-test; $comparison with Serum triglycerides values

between groups and p-value was calculated by using unpaired t-test; &comparison with HDLc values between groups and p-value was calculated by using unpaired t-test; ^comparison with LDLc values between groups and p-value was calculated by using unpaired t-test, !comparison with LDLc values between groups and P-value was calculated by using unpaired t-test.

Discussion

Persons with T2DM shows negative impact on health care costs, mortality and morbidity globally, hence this disease has to be controlled or prevented at an early stage to over the come the effects. If properly treated, prediabetes stage not progress to diabetes and may revert to normal as well. Progression to diabetes from prediabetes can be controlled by pharmacotherapeutic agents along with lifestyle interventions. Several highly effective pharmacological agents are available to control the abnormal blood glucose levels, however, available agents are either patients are not well tolerated due to adverse effects or economically not affordable. From the centuries, traditional medicinal plant sources are using to control the diabetes as alternative therapies. Researchers tried and still trying numerous plant materials to control the diabetes, a significant amount of research with Fenugreek showed best in terms of efficacy and safety out of the available herbs. Although numerous studies were conducted in animals and humans to evaluate the hypoglycemic and hypolipidemic effects of Fenugreek with type 1, type 2 diabetes and prediabetes. Studies which shows the hypoglycemic and hypolipidemic effects of Fenugreek on prediabetes is not well studied or understood.

A total of 140 subjects were completed entire study period in each group and analyzed the data. Nearly three-quarters of study participants were reported as overweight at baseline in both the groups. Weight loss strategies which reduce the fat mass can reduce the lipid oxidation and an enhancement of glucose metabolism. Several studies showed that after weight loss, insulin secretion and insulin concentration in plasma significantly decreased. In the present study, Fenugreek has been administered along with dietary medications which includes exercise may improve the glucose metabolism. Most of the study participants (90-95%) were either low or middle socioeconomic status, as these findings are consistent with the place of study. The present study was conducted in tertiary care teaching hospital. According to a study to explore the association of early life socioeconomic conditions with prediabetes. Results showed that early life socioeconomic subjects had 1.56 times higher odds of prediabetes (95% CI) = 1.21-2.02) and 1.61 times higher odds of T2DM (95% CI = 1.31-1.99)[9]. Subjects with low socioeconomic conditions such as poor education, low income and life style changes are at higher risk of prediabetes and diabetes compared to subjects with higher socioeconomic status[10]. Furthermore, obesity or overweight, smoking and alcohol use, physical inactivity are linked to early life socioeconomic status which reflects their health status during later life.

Sub-group analysis was performed on categories of age which reveals that no patient has been reported prediabetes under the age of 30 years in both the groups. Half of the patients (Group 1: 55.7% and Group 2: 52.9%) were in the age group of 40-50 years. ICMR–INDIAB conducted a study in the states of

Tamilnadu, Maharashtra, Jharkhand and Chandigarh and reported the possible risk factors for prediabetes which includes age (OR 1.2 [95% CI 1.1,1.3, $p < 0.001$]), family history of diabetes (OR 1.2 [95% CI 1.0,1.5, $p = 0.045$]), abdominal obesity (OR 1.7 [95% CI 1.4,1.9, $p < 0.001$]), hypertension (OR 1.3 [95% CI 1.1,1.5, $p = 0.005$]) and income status (OR 1.2 [95% CI 1.1,1.3, $p < 0.001$]) were significant risk factors.

In the present study, subjects showed slightly higher HbA1c levels at baseline in both the study. Change of HbA1c levels in dietary modification + Fenugreek group showed significant fall at 3, 6 and 12 months. A total of 12.28 percentage of HbA1c has come down after 12 months of Fenugreek treatment.. Adding Fenugreek along with dietary modifications has significantly ($P<0.01$) control and improve the HbA1c levels over time. A study conducted and reported that 21% risk reduction (95% CI: 17% to 24%, $P<0.0001$), can be achieved with any endpoint related to diabetes witheach 1% reduction in mean HbA1c[11]. Individual risk factors can be reduced to 37% for microvascular complications (33% to 41%, $P<0.0001$), 14% for myocardial infarction (8% to 21%, $P<0.0001$),21% for deaths related to diabetes (15% to 27%, $P<0.0001$).

A randomized controlled study on Diabetes and reported a significant improvement with fenugreek treatment after 3 months follow-up in which HbA1c lowered by 0.92% (95% CI, 0.34-1.50), $p < 0.001$ as compared to medical care alone 0.42% (95% CI, 0.11-0.94), $p = 0.12$ in poorly controlled diabetic patients[12]. Another randomized trial conducted and reported that statistically significant difference in HbA1C values were observed at 6th month onwards[13]. In the present study, serum cholesterol, triglycerides, HDL, LDL and VLDL levels were significantly ($P<0.001$) improved with Fenugreek treatment at the end of 1 year. More than 20.0% of LDLc and VLDLc were decreased in fenugreek group compared to dietary modification alone group. These findings are in agreement with other studies in which triglycerides and cholesterol levels were significantly ($P<0.05$) decreased with Fenugreek treated animal models compared to untreated animals. In contrast to the present study serum cholesterol and triglyceride levels were almost similar in control and Fenugreek treated groups at the end of study period. Perhaps, even small changes in cholesterol and triglyceride serum levels could be due to the fact that the mean data for these variables are already in the normal range[14].

A total of 28.8% HDLc increased in Fenugreek treatment group compared to control group in the present study. A study conducted and reported that Fenugreek seed powder solution had pronounced effects in improving lipid metabolism in type-2 diabetic patients with no adverse effects[15]. Few studies are in contrast to the present study which shows that controls and Fenugreek treated groups had no significant changes in HDLc throughout the study period[14]. The possible and most accepted mechanism of action of Fenugreek seeds which act as a lipid lowering agent is as it contains a gel-like soluble fiber which binds with bile acids in the plasma which lowers the triglyceride and LDL cholesterol levels[17].Strengths of the study includes, this is a prospective parallel randomized study included both men and women with different socio economic statuses with compromising selection criteria defined earlier. Bias was appropriately controlled at every stage of the study which includes experimental, instrumental,

investigator, observational and methodological bias. High sample size was calculated to increase the power of the study. Very limited studies are published as of now to investigate the exact effect of Fenugreek on prediabetes. Probably, this is one of the systematic long term studies with Fenugreek on prediabetes. Again very limited studies are reported the incidence of conversion rate from prediabetes to diabetes with high variation. The present study addressed the exact incidence in a controlled manner. Subjects who are recruited to the control group also equally monitored and received health advice, frequent checkups, and dietary plans at each follow up visits. Study participants who dropped out before the deadline of the study was not included for the analysis.

Limitations of the study

The present study is not blinded and masked the treatment. Safety profile was not assessed. Study duration can be extended to 2 years to know the exact safety profile of Fenugreek. Cost-effectiveness and cost-utility analysis was not included as objectives.

Conclusion

This study demonstrated that Fenugreek delays the progression of diabetes from prediabetes, Fenugreek improved the lipid profile and act as a hypocholesterolemic agent.

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