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Original article

Effect of chronic Fenu-fibre supplementation in freshly diagnosed Type 2 Diabetic Subjects

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ABSTRACT

Background: Fenugreek is known for its anti-diabetic properties. Although different compounds in it have been proposed to be active, the actual active component(s) is(are) still to be established. **Objective:** To find out the antidiabetic effect of fenu fibre in freshly diagnosed type2 diabetic subjects. **Materials and Methods:** Anti-diabetic properties of fenugreek fibre, the outer coat of the fenugreek seeds, were assessed by supplementing it to freshly diagnosed (3-6month duration) type 2 Diabetes Mellitus (T2DM) patients for a duration of 45 days. **Results:** Chronic supplementation of fenu - fibre @ 15g/day, significantly reduced the fasting plasma glucose and insulin resistance as assessed by HOMA–IR, whereas beta cell function (HOMA β%) was significantly increased. It decreased the area under curve (AUC) of glucose during the oral glucose tolerance test (OGTT) but not plasma insulin: fasting or post glucose load, suggesting improved insulin sensitivity. Plasma HDL cholesterol was increased whereas plasma total cholesterol and triglycerides were unaffected, indicating a marginal effect on lipid profile. **Conclusion:** Supplementation of fenu-fibre to freshly diagnosed T2DM patients improved their glycaemic status and increased insulin sensitivity / beta cell function may underlie this effect.

KEYWORDS: Fenu-fibre, type2 Diabetes

INTRODUCTION

Incidence of lifestyle diseases including metabolic disorders has been increasing recently in parallel with rapid economic development, even in developing countries like India. As per IDF , approximately 366 million people suffered from diabetes globally in 2011 and the number projected for 2030 is around 552 million [1].Treatment of metabolic diseases involves the improvement of dietary habits and increasing physical activity, although it is difficult to modify one's life style. In such cases, natural products have been a source of medicinal treatment for thousands of years.

Fenugreek (*Trigonellafoenum-gracium)* is native to Eastern Mediterranean, Central Asia and Ethiopia. It is very much cultivated in India, Pakistan and China and fenugreek seeds are rich in fibre (48g%) [2].The term Dietary fibre, is mainly associated with non-digestible, but fermentable carbohydrate mixtures and lignins, which are neither hydrolyzed nor absorbed in the upper part of the mammalian gastrointestinal tract[3]. Epidemiological data indicate an inverse relationship between dietary fibre intake and prevalence of diabetes [4].

However, earlier studies have demonstrated the metabolic effects of different types of fibre may be different. For eg, Guar gumfrom cluster bean, a gel forming galactomannan polysaccharide has been shown to reduce post-prandial glucose and insulin levels in healthy volunteers [5,6]. Indeed, the soluble fibre derived from fenugreek seeds has been identified as galactomannan, just like the solublefibre of guar seeds, psyllium husk etc[7]. Earlier studies from NIN and elsewhere [8,9] have suggested that the fibre fraction of fenugreek seeds may be responsible for its hypoglycaemic action. Indeed, fibre rich food and gums [10] have been reported earlier to control glycaemic status in diabetic subjects.

High fibre diets are effective in diminishing insulin secretion, lowering blood glucose and are thus beneficial in treating diabetics, particularly those with type 2 diabetes. A combined high carbohydrate, high fibre diet may blunt the

post prandial elevation of blood glucose and reduce insulin requirement[11]. A fibre rich meal is metabolised slowly and nutrient absorption is delayed and occurs over a longer period[12].The beneficial effects of high fibre diet (intake >25g/day in women and>38g/day in men)[13], can mainly be attributed to the viscous and gel forming properties of soluble dietary fibre [14]. Earlier studies showed that consumption of soluble dietary fibre significantly reduced serum and liver cholesterol levels as well in rats [15,16]. Incorporation of isolated soluble fibre from fenugreek seeds in the diet (at a level of 5%) showed hypo-lipidemiceffect in WNIN/Gr-Ob mutant obese rats and also improved their plasma glucose levels by increasing their insulin sensitivity[17].

Despite robust literature in experimental animal models on the beneficial effects of fenugreek seed powder, its solvent extracts and isolated fibre (soluble and insoluble)to prevent or control diabetes, there is no information on its effects in the diabetic patients. Therefore, this study was conducted in freshly diagnosed diabetic subjects to evaluate the anti-diabetic effects of fenu- fibre, the de-bitterized outer coat of the fenugreek seeds(husk) which is commercially available. In addition, the effects of fenu-fibre if any on the development of other complications like constipation, acidity, weight gain/loss and heart burn etc were also evaluated.

MATERIALS AND METHODS

Fenugreek Fibre: Husk of fenugreek seeds: "fenu-fibre", a product developed based on the earlier research at the National Institute of Nutrition, Hyderabad, was purchased from M/S Natural Health Care, Bangalore, India. It was stored at room temperature in air tight containers till use.

Diabetic patients: Twenty five diabetic patients, aged between 30 and 55 years, who were diagnosed to be diabetic of not more than 3-6 months duration, with fasting glucose≥126mg/dl or 2 hr Post prandial (PP) glucose ≥ 200mg/dl)and free from any serious complications, were recruited for the study. These patients were drawn from the diabetic outpatient clinics at Yashoda hospital and Sunshine hospital, Secunderabad, Telangana state (India). Of these 17 were men and 8 were women. Informed consent was obtained from each patient before the study. The approval of the ethical committee of NIN, Hyderabad was obtained for the study. The subjects underwent clinical checkup at regular intervals.

Initially the patients were on a washout period for 15 days during which they were on their routine diets and this was considered as self-control period, specially for the estimation of baseline parameters. After the wash out period, an oral glucose tolerance test (OGTT) was performed on each patient, with 75 g of oral glucose load. Then the patients were asked to continue their normal home diet but containing the prescribed amounts of protein, fat, carbohydrate and dietary fibre. In addition they were asked to consume 15g of fenu-fibre per day in three divided doses according to the diet chart provided (i.e. 5 g each before breakfast, lunch and dinner).

Each study subject was supplied 500 grams of fenu-fibre (commercially available) in an air tight container to be stored at room temperature. Subjects were asked to soak about 5-7 grams of fenu-fibre in half a glass of drinking water for ten minutes, to allow the fiber to absorb water and form a gel, which being slimy would be easy to chew and swallow. The patients were asked to consume the gel, half an hour before the consumption of the regular meal (break-fast, lunch or dinner) and they were asked to continue the same prescribed diet for the entire study period of 45 days. Drug intake if any, of the patients was stopped for the duration of the study. For each subject, fasting plasma glucose and insulin levels were determined at base line (after the washout period) and at the end of 45 days of supplementation of fenu-fibre. In addition, lipid profile was determined in the plasma samples after an overnight fast at both the time points referred above. At the end of fenu-fibre treatment regime of 45 days, fasting plasma glucose, insulin, HOMA IR, HOMA β% and the OGTT were repeated in each subject and the AUC of glucose and insulin during the OGTT were determined.

Biochemical Analysis:

Blood samples were collected in heparinized /EDTA tubes and plasma was separated and stored at – 80 ^{0}C till use. Fasting Plasma Glucose and Lipid Profile were determined using the kits purchased from M/S Biosystems. Fasting plasma Insulin and insulin during 30,60 and 120 minutes of the OGTT were determined using the Radio-Immuno Assay kit from BRIT, Mumbai, India. HOMA IR (Homeostatic Model Assessment for Insulin Resistance) was calculated using the fasting plasma Glucose (mmol/l) and fasting plasma Insulin (μunits/ml) as described earlier [18],while the β-cell function (HOMA β %)which is considered to be a good measure of β-cell function [19], was computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5. The area under the curve for glucose and insulin during the OGTT were calculated using the trapezoid rule and the ratio of AUC glucose to AUC insulin during the OGTT was computed as a measure of post prandial insulin sensitivity / resistance.

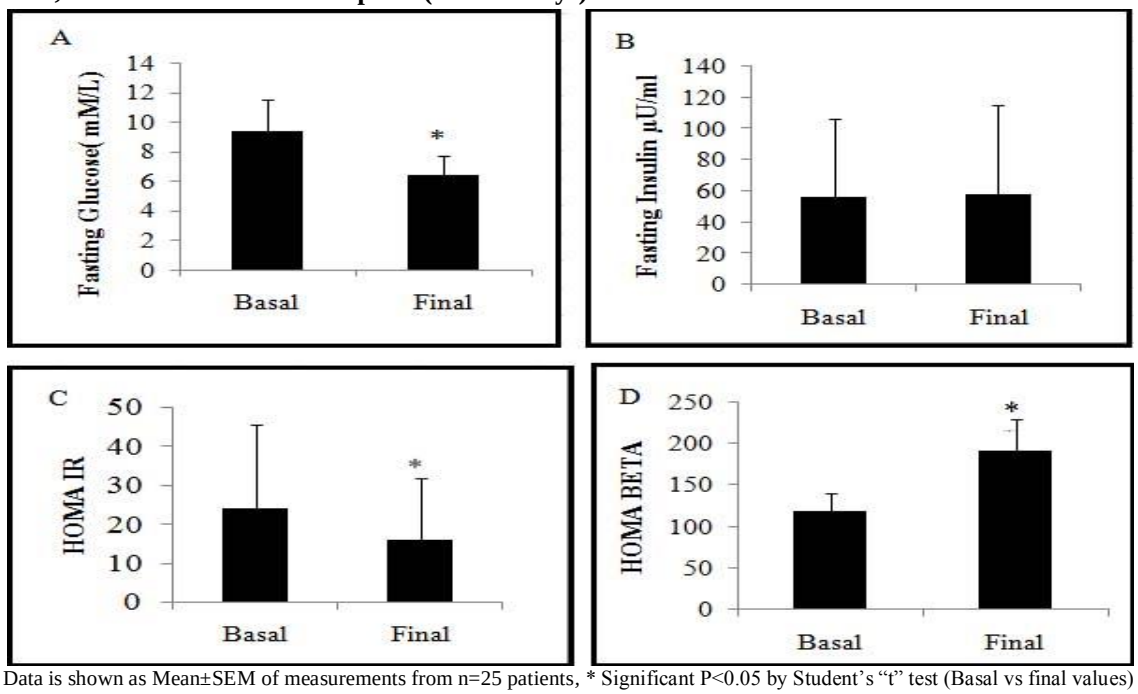
RESULTS

There were no complaints such as poly urea, giddiness, weakness and tingling numbness in any of the patients during the supplementation of fenu-fibre for 45 days. Indeed, a few subjective parameters like constipation, acidity, heart-burn and body weight were all reportedly reduced during this period.

After the wash out period, the patients had high fasting plasma glucose (~ 10 mM) and insulin (~50 μU / ml) levels (compared to non-diabetic controls) and as a consequence their HOMA IR values were markedly high (>22) (Fig 1), indicating their high insulin resistance and diabetic status. On the other hand, HOMA β%, a measure of the β cell function was within the range reported for normal subjects.

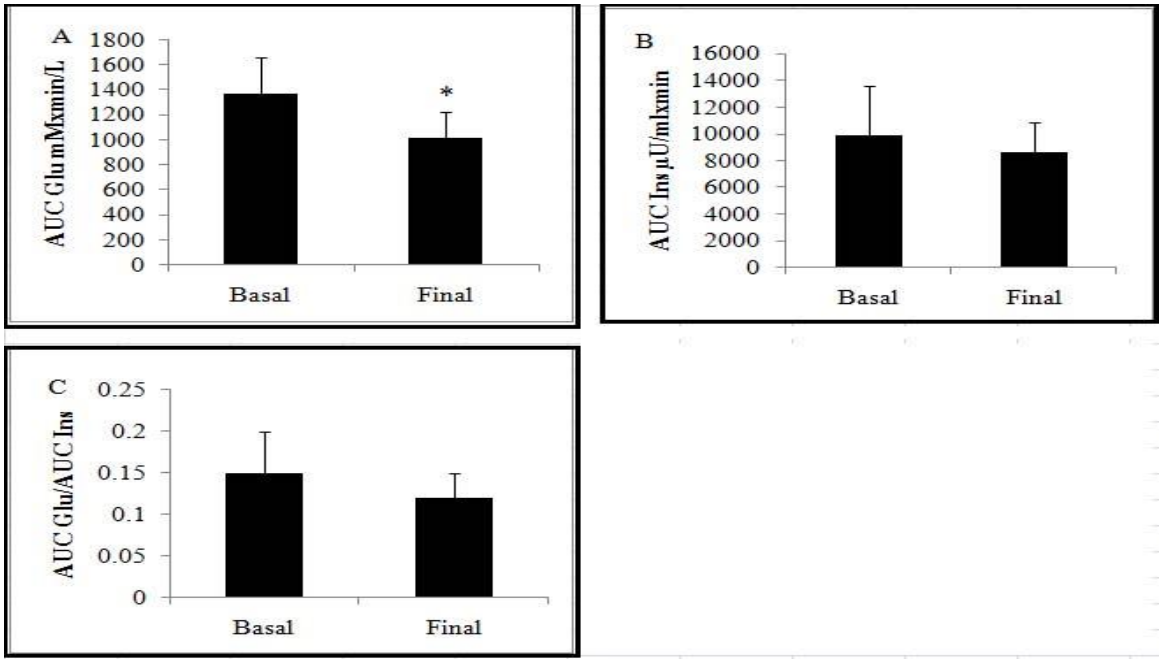
In line with their high fasting glucose, insulin and HOMA IR levels at the baseline (compared to non –diabetic controls), at baseline , the AUC of glucose and insulin during OGTT were also high confirming that the patients were hyperglycaemic/ diabetic and insulin resistant post prandially also (Fig 2).

Figure1:Effect of Fenu fibre supplementation in diabetic subjects on Fasting glucose, Fasting Insulin, HOMA-IR,HOMA-Beta, at basal and at final time point (after 45 days)



Data is shown as Mean±SEM of measurements from n=25 patients, * Significant P<0.05 by Student's "t" test (Basal vs final values)

Figure 2: Effect of Fenu fibre supplementation in diabetic patients on Glucose tolerance and Insulin resistance indices at basal and final time point (after 45 days).



Data is shown as Mean±SEM of measurements from n=25 patients, * Significant P<0.05 by Student's "t" test (Basal vs final values)

Supplementation of fenu-fibre to the patients for 45 days, significantly lowered their fasting plasma glucose levels to ~ 5-6 mM(P<0.05) (Fig1) but had little effect on their fasting plasma insulin levels. That their HOMA IR values were significantly reduced (p<0.05) compared to those at the baseline, indicate that fenu-fibre treatment increased their insulin sensitivity /decreased their insulin resistance. Despite no change in fasting plasma insulin levels, HOMA β% was significantly (P<0.05) increased in them compared to the values before treatment. This, appears to suggest an increased sensitivity of β cells to circulating glucose so that their insulin secretion is unaffected inspite of lowered circulating glucose levels.

In line with their fasting glucose and insulin levels, the Area under curve of glucose during the OGTT was significantly reduced (P<0.05) in these subjects after fenu-fibre treatment (Fig 2) indicating improved post prandial glucose clearance. That during the OGTT, the AUC glucose decreased despite no significant change in AUC insulin seems to suggest that the increased post prandial glucose clearance was perhaps due to / associated with increased target organ insulin sensitivity and / or decreased intestinal glucose absorption.

Our finding that at the baseline (i.e. after the wash out period), plasma lipid profile (triglycerides, total cholesterol

and HDL cholesterol) of the study patients was within the normal range reported for that age group, is in line with our inference that their diabetes was of recent origin. Although fenu-fibre supplementation for 45 days did not affect their serum triglycerides and total cholesterol levels, their HDL cholesterol levels were significantly increased($P<0.05$), probably suggests favorable modulations in cholesterol metabolism(Table 1) in these patients.

Table 1:Effect of Fenu fibre supplementation in diabetic subjects on lipid profile

S.no	Parameter	Basal(mmol/L)	Final(mmol/L)	P Value
1	Plasma Cholesterol	4.62±0.72	4.46±0.84	NS
2	Plasma Triglycerides	1.37±0.64	1.35±0.65	NS
3	Plasma HDL cholesterol	0.71±0.61	0.80±0.25	* P<0.05

Data given is Mean±SEM of measurements from n=25 patients, NS- Non significant, * Significant at P<0.05 by Student's "t" test

DISCUSSION

The term dietary fibre, is associated with the non-digestible, but fermentable carbohydrate mixtures and lignins, which are neither hydrolyzed nor absorbed in the upper part of the gastrointestinal tract [3]. Dietary fibre, constitutes between 45 and 50% of the fenugreek seed's dry weight[20,21] ; insoluble fibre constitutes 32% while the soluble fibre accounts for 13 % of the seed's dry weight [20]. Fenugreek fibre thickens the ingested food to form a gel in the stomach, trapping fat and sugar and also the starch hydrolysing amylases thereby slowing down carbohydrate digestion and sugar absorption [22]. Indeed ,fenugreek fibre is reported to reduce the rate of glucose absorption and also delay gastric emptying, preventing the rise in blood sugar levels following a meal [23]. Results from previous studies, which evaluated the effects of dietary fibre on glycemic control in type 2 diabetic patients have been inconsistent [24,25].

This lack of consistency in some studies makes the data difficult to interpret. For example, in some previous studies [24,25] high-fibre diet had lower fat and higher carbohydrate content than the low-fibre diet. Further, in some other studies, interpretation of results was confounded by the short duration of intervention[26,27], lack of random assignment to the sequence of feeding high and low fibre diets[26,27] and the unexplained weight loss during the consumption of high-fibre diet. [27] Fenu fibre is the only fibre without the oils or the bitterness. Indeed , every 10 g of Fenu fibre powder contains, approx. 3 g Soluble fibre, 2 g Insoluble fibre and 3 g Protein with Zero Fat (= No High-Calories) and zero steroidal saponins (=No weight-gain).

In the present study incorporation of fenu-fibre in the diet @15g/day for 45 days significantly decreased the fasting glucose in the diabetic patients. Considering the importance of gluconeogenesis in maintaining fasting blood glucose levels, our findings appear to suggest a modulation (decrease) of gluconeogenesis in the fenu-fibre supplemented patients, which needs to be verified. That fasting glucose levels were decreased without any change in fasting insulin levels suggests an increased insulin sensitivity, which indeed is evident from the significantly lower HOMA IR values. Although HOMA β% was significantly increased by fenu-fibre feeding, it was intriguing that fasting plasma insulin levels were unaffected. Considering that HOMA-β% indicates the beta-cell secretory capacity and higher the value, greater is the insulin secretion [28], the unaffected fasting plasma insulin levels in fenu-fibre treated patients despite their significantly lower fasting plasma glucose, may be inferred as an increased beta cell function i.e. unaffected insulin production despite significantly lower fasting plasma glucose levels. This indeed needs to be verified by assessing the function / expression of glucose transporter 2 (Glut 2), the glucose sensors in the beta cells.

That in fenu-fibre supplemented patients AUC glucose during the OGTT was significantly decreased without any significant change in AUC insulin is also in line with our similar findings on fasting plasma glucose and insulin after fenu-fibre supplementation. The significantly lower AUC glucose during OGTT could either be due to decreased intestinal absorption of glucose and / or increased clearance of circulating glucose, both of which are known to regulate post prandial glucose levels [29]. That during OGTT, AUC glucose was decreased despite no significant change in AUC insulin although suggests increased insulin sensitivity of the target organs (eg; muscle and adipose tissue) and the consequent increased clearance of circulating glucose post-prandially, it could also be due to decreased intestinal glucose absorption, which needs to be confirmed. That AUC insulin was unaffected by fenufiber supplementation, is in agreement with our finding / inference on its effect on fasting plasma insulin vis a vis fasting plasma glucose levels.

Taken together, our observations on fasting plasma glucose, insulin and AUC of glucose and insulin during OGTT in the fenu-fibre treated type 2 diabetic patients seem to suggest increased function of beta cells as evident from unaffected plasma insulin levels despite significantly lower plasma glucose levels, both fasting and post prandial. Regardless of the underlying mechanisms(s), it appears true that chronic fenu-fibre supplementation to type 2 Diabetic patients improved their glycemic status both under fasting and post prandial conditions and increased their beta cell function *albeit* without any change in circulating insulin levels.

That chronic fenu-fibre supplementation in diabetic patients did not affect fasting or post prandial insulin levels is in line with a previous study that the SDF(Soluble Dietary Fiber) fraction did not stimulate insulin secretion during feeding [30]. 4-hydroxyisoleucine, previously isolated as an insulinotropic agent from fenugreek seeds [31] probably had been excluded from the SDF fraction used by the earlier researchers [30]. Interestingly, the SDF fraction has been

reported to increase the glycogen content significantly in the liver of type 2 diabetic rats after 28 d treatment [32].

However, since hepatic glycogen is markedly decreased in human diabetics and normalized by insulin treatment [33,34,35], it supports the inference that administration of the SDF fraction may also have increased insulin action (glycogen synthesis ?) in the liver. Indeed the operation of a similar mechanism cannot be ruled out at this juncture in diabetic patients supplemented with fenu-fibre. Only a few, well-controlled studies have evaluated the hypoglycaemic effects of increasing the intake of dietary fibre, specially using preparations of refined concentrated fibre or unfortified food and the results have indeed been inconsistent[36,37].

Unlike the hypo-cholesteremic effects reported earlier of the fenugreek seeds[38], it was surprising that the fenu-fibre used in the present study, did not reduce plasma total cholesterol and triglyceride levels. The discordance of our findings with previous reports in fenugreek seed powder may suggest that the hypo-cholesteremic effect of the fenugreek seed in the previous study was perhaps not due to its fibre component. It is interesting that our study is in partial agreement with some previous ones that in normal subjects there was no effect of dietary fibre on plasma triglyceride concentrations [39].Notwithstanding these discrepancies, it is however interesting that chronic supplementation of fenu-fibre to diabetic patients, significantly increased their HDL cholesterol level. Although, the underlying / associated mechanism(s) by which the HDL cholesterol levels are raised , are not clear at present, our findings if confirmed, shall be of immense importance in the utility of fenu-fibre in modulating / alleviating adverse changes in lipid metabolism that normally ensue as the diabetes progresses.

CONCLUSION

In conclusion, chronic, high intake of dietary fibre in the form of fenu-fibre, lowered plasma glucose under fasting and post prandial conditions in freshly diagnosed diabetic patients. That it did so without affecting insulin secretion / levels, suggests that it could be due to decreased hepatic gluconeogenesis and / or increased glycogen synthesis and / or decreased intestinal absorption and / or increased clearance of circulating glucose post-prandially due to increased target organ insulin sensitivity as appropriate. Interestingly our results also indicate that fenu-fibre supplementation significantly increased beta cell function *albeit* without affecting plasma insulin levels and also increased the HDL, the good cholesterol. Over all our results appear to advocate its use at least as an adjuvant in the Diabetic treatment.

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