Effect of Fenugreek Consumption with Metformin Treatment in Improving Plaque Index in Diabetic Patients

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Abstract

Aims and Objectives: The aim of this study is to compare the efficacy of metformin and fenugreek seed powder as an adjunct to scaling and root planing (SRP) with the effect achieved using SRP and metformin alone by assessing their respective effects on periodontal parameters, glycemic status, and inflammatory marker. Materials and Methods: Eighty patients were included in this study who were further divided into two groups. Each group consisted of 40 patients. Group 1 patients included chronic periodontitis with uncontrolled type 2 diabetes mellitus (DM), who received SRP and treatment with metformin. Group 2 patients included chronic periodontitis with uncontrolled type 2 DM, who received SRP, metformin plus fenugreek powder. Periodontal parameters such as plaque index (PI), gingival index, bleeding on probing, pocket depth, and clinical attachment levels were evaluated at baseline and 1 month after nonsurgical periodontal therapy. Results: On intragroup comparison of clinical parameters at baseline and after treatment, a statistically significant reduction was observed for both Group 1 and Group 2 patients. When intergroup comparison was done after treatment, significant reduction was observed only for PI (P < 0.0031). On intragroup comparison was done for fasting blood sugar (FBS) and HbA1c before and after nonsurgical periodontal treatment, there were statistically significant changes seen in both the groups for FBS (P < 0.001) and for HbA1c in Group 2 patients alone. The level of IL-6 also reduced after treatment compared to baseline values (P < 0.001). Conclusion: The direct effect of fenugreek on the FBS level could attribute to the changes in the PI and decrease in the inflammation. Thus, the study showed that fenugreek seeds could be used as an adjuvant in chronic periodontitis patients to control type 2 DM and inflammatory marker IL-6.

Keywords: Chronic generalized periodontitis, fenugreek seeds, glycosylated hemoglobin, interleukin-6, metformin, type 2 diabetes mellitus

Introduction

Periodontitis is a destructive inflammatory disease of the supporting tissues of the teeth and is caused either by specific microorganisms or by a group of specific microorganisms, resulting in progressive destruction of periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession, or both[1] The association of periodontal infection with organ systems such as cardiovascular system, endocrine system, reproductive system, and respiratory system makes periodontal infection a complex multiphase disease.[2] Periodontal disease is an inflammatory disease produced as a result of microbial aggression. Although microbial flora is permanently present in the oral cavity and in the gingival area, the beginning of periodontal disease is defined by the existence of periodontal pathogens and susceptibility of host organism. Diabetes and periodontal disease share a bidirectional relationship. Diabetes influences the progression of periodontitis and poor glycemic control leads to worsened periodontal condition and vice versa. Nonsurgical therapy of periodontal disease has shown to improve the glycemic status of diabetic individuals.

Interleukin-6 (IL-6) is an IL that acts as both a proinflammatory cytokine and an anti-inflammatory myokine. In humans, it...
is encoded by the IL-6 gene.\textsuperscript{[3]} IL-6 is secreted by T cells and macrophages to stimulate immune response leading to inflammation. In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on tumor necrosis factor alpha and IL-1, and activation of IL-1ra and IL-10. Serum IL-6 levels have also been found to be associated with insulin resistance and diabetes. In nondiabetic older populations and healthy, middle-aged, western population, higher serum IL-6 levels correlated with increased insulin resistance.\textsuperscript{[4,5]} In individuals with impaired glucose tolerance, type 2 diabetes, or the metabolic syndrome, serum IL-6 levels were also found to be higher compared with those with normal glucose tolerance or those who did not meet the criteria for the metabolic syndrome.\textsuperscript{[6]} Liu \textit{et al.} recently reported that elevated IL-6 levels are also associated with an increased risk of clinical diabetes in a large prospective study of postmenopausal women who participated in the Women’s Health Initiative in the United States.\textsuperscript{[7]}

IL-6 is the major regulatory cytokines for human C-reactive protein (CRP). CRP is perhaps the most common serum marker of inflammation. If systemic inflammation is causally linked to diabetes development, anti-inflammatory treatment would seemingly be beneficial. Many studies have shown dramatic elevation of IL-6 levels in inflammatory periodontal lesions and IL-6 is also thought to be a useful indicator or a diagnostic marker for periodontitis.\textsuperscript{[8-10]}

Fenugreek seeds have been shown to have an effect on cholesterol and blood sugar\textsuperscript{[11]} and are used for the treatment of diabetes mellitus (DM) in many parts of the world, including India.\textsuperscript{[12]} These seeds are high in soluble fibers, saponins, trigonelline, diosgenin, and 4-hydroxyisoleucine.\textsuperscript{[13,14]} Soluble fibers like galactomannan present in fenugreek seed help in lowering blood sugar by slowing down digestion and absorption of carbohydrates. The leaves and seeds of fenugreek are used either as extracts or powder form for medicinal use. Therefore, there has been a greater source of awareness of the antidiabetic properties of fenugreek. Antidiabetic properties are attributed mainly to galactomannan, 4-hydroxyisoleucin (4-OH-Ile), 4-hydroxyisoleucine is a natural nonproteinoenic aminoacid possessing noninsulinotropic biologic activity causing increased glucose induced release of insulin through a direct effect on the isolated islets of Langerhans.\textsuperscript{[15]} In humans, fenugreek seeds exert hypoglycemic effects by stimulating glucose-dependent insulin secretion from pancreatic beta cells, as well as by inhibiting the activities of alpha-amylase and sucrase, two intestinal enzymes involved in carbohydrate metabolism.\textsuperscript{[16,17]} Since diabetic patients have increased inflammatory cytokines which modify the risk of diabetes, this study was carried out to compare the effect of metformin and fenugreek seed powder as an adjunct to nonsurgical periodontal therapy on the glycemic status and inflammatory cytokine IL-6 level.

\section*{Materials and Methods}

The patients were randomly selected from the outpatient clinic of the Department of periodontics, Thai Moogambigai Dental College and Hospital, Maduravoyal, Chennai, Tamil Nadu, India. Written consent was obtained from each participant. All participants completed the study. The study protocol was approved by the ethical committee of Dr. M.G.R University, Maduravoyal, Chennai, Tamil Nadu, India, in accordance with the Declaration of Helsinki, as revised in 2000.

This study consisted of 80 participants which is divided into two groups as follows:

\begin{itemize}
  \item Group 1: 40 participant with chronic periodontitis with uncontrolled type 2 DM treated with metformin alone
  \item Group 2: 40 participant with chronic periodontitis with uncontrolled type 2 DM treated with metformin along with fenugreek seed powder as an adjuvant to scaling and root planing (SRP).
\end{itemize}

In the selected patients, detailed medical history was recorded. All the patients involved in this study had uncontrolled DM. The treating physicians consent and details of the patients regarding diabetes control were also obtained. The uncontrolled DM was defined based on glycosylated hemoglobin (HbA1c) values >8 mg/dl. The history of these diabetic patients selected for the study was >5 years. Clinical parameters were recorded and blood samples were obtained from the participants of both groups at baseline and 1 month after nonsurgical periodontal therapy. The duration of the study to procure 80 patients was 3 months.

\section*{Inclusion criteria}

\begin{itemize}
  \item The inclusion criteria in the study were patients who were suffering from chronic periodontitis with uncontrolled type 2 DM
  \item They should have at least 30\% of the sites with clinical attachment level (CAL) \(\geq 4\) mm, pocket depth (PD) of \(\geq 5\) mm, and bleeding on probing (BOP).
\end{itemize}

\section*{Exclusion criteria}

\begin{itemize}
  \item Patients who had undergone periodontal treatment in the past 6 months
  \item Those with a history of antibiotic administration within the past 3 months
  \item Those with \(<20\) remaining natural teeth
  \item Participants who were pregnant
  \item Participants with a history of smoking, liver disease, and insulin therapy
  \item Participants with tobacco and alcohol consumption.
\end{itemize}

\section*{Periodontal treatment and clinical measurements}

All patients were subjected to a periodontal examination performed in six sites per tooth excluding the third molar. Periodontal parameters such as:

\begin{itemize}
  \item Plaque index (PI) (Silness and Loé 1964)
  \item Gingival index (GI) (Loé and Silness 1963)
  \item BOP (Muhlemann and Son 1971).
\end{itemize}

PD and CAL were evaluated at baseline and 1 month after treatment. Blood samples were collected after a minimum of 10 h
of overnight fasting for all individuals at baseline and 1 month after treatment. After recording the periodontal status, patients received oral hygiene instructions and underwent full mouth nonsurgical periodontal treatment comprising SRP under local anesthesia. Fenugreek seeds were procured from IMPCOPS Ltd., (Chennai, Tamil Nadu, India). The seeds were air dried for 7 days at room temperature. The dried seeds were weighed and ground using high-speed grinder. This powder was stored in airtight container and kept away from heat, moisture, and sunlight. Group 1 patients were advised to take their regular treatment protocol, that is, metformin tablets as per the instruction of the physician, whereas patients in Group 2 were provided with fenugreek powder along with measuring scoops to measure 12.5 mg of the powder and to consume the powder during morning and afternoon before food along with regular metformin regimen. After the periodontal treatment, a professional plaque control program was performed twice a month, which consisted of supragingival plaque removal and reinstruction of oral hygiene procedures. During this experimental period, patients were questioned about changes in medications related to diabetes therapy, use of anti-inflammatory or antibiotic, and alteration of lifestyle, including exercise and diet.

**Sample collection**

Venous blood samples were collected in the morning after an overnight fast. Samples were analyzed for fasting blood sugar (FBS) and HbA1c. The samples were centrifuged at 3000 rpm for 15 min to separate the plasma. Fasting plasma glucose level was measured using the glucose oxidase-peroxidase method. The HbA1c concentration was measured using Column method. Serum samples were analyzed for IL-6 using a highly sensitive sandwich ELISA test kit (BIO SCIENTIFIC, USA) with minimum detectable concentration of 8 pg/ml.

**Statistical analysis**

Statistical analyses were performed using a software program (Version 16 produced by SPSS, IL, IBM). Intragroup comparison of variables was calculated by paired t-test and Intergroup comparison was done by unpaired t-test. Intragroup comparison of mean reduction from baseline for all the parameters (PI, GI, BOP, PD, CAL, FBS, HbA1c, and IL-6) was analyzed using the unpaired t-test.

**Results**

When intragroup comparison was made for all the clinical parameters, there is statistical significance in both the groups [Table 1]. When intergroup comparison was made, there was statistical significance observed only for PI (P < 0.0031) [Table 2]. The glycemic status was measured using FBS and HbA1c values. When intragroup comparison was done for FBS and HbA1c before and after nonsurgical periodontal treatment, there were statistically significant changes observed in both the groups for FBS (P < 0.001) [Table 3] and for HbA1c in Group 2 patients alone. Similarly, when intergroup comparison was done for FBS and HbA1c individually, there was statistical significance observed only for FBS after treatment (P 0.004) [Table 4]. When intragroup comparison was done for IL-6, at baseline, and after nonsurgical periodontal treatment, there was a statistical significance observed (P < 0.001) [Table 5]. Similarly, when intergroup comparison was done for IL-6, there was no statistical significance seen [Table 6]. Intergroup comparison of mean reduction from baseline for all the parameters shows significance only for PI and FBS (P = 0.0031 and 0.004) [Table 7].

**Discussion**

Many proinflammatory cytokines play a central role in inflammatory reaction and were shown to increase the risk of type 2 DM. In this regard, substantial experimental evidence and many cross-sectional data suggest that IL-6 and CRP, two sensitive physiological markers of subclinical systemic inflammation, are associated with hyperglycemia, insulin resistance, and overt type 2 DM. IL-6, a major pro-inflammatory cytokine, is produced in a variety of tissues including activated leukocytes, adipocytes, and endothelial cells. In rodent models of glucose metabolism, the in vivo infusion of recombinant IL-6 has been shown to induce gluconeogenesis subsequent hyperglycemia and compensatory hyperinsulinemia.

<table>
<thead>
<tr>
<th>Table 1: Intragroup comparison of clinical parameters at baseline and after treatment using paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
</tr>
<tr>
<td><strong>Plaque index</strong></td>
</tr>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After treatment</td>
</tr>
<tr>
<td>P=0.0039 sig</td>
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<tr>
<td>Mean reduction</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After treatment</td>
</tr>
<tr>
<td>P=0.0052 sig</td>
</tr>
<tr>
<td>Mean reduction</td>
</tr>
</tbody>
</table>

SD - Standard deviation, CAL - Clinical attachment level, Sig - Significance NS - Non significance, P<0.05 is considered significant.
Table 2: Intergroup comparison of mean and standard deviation of clinical parameters after treatment

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Groups</th>
<th>Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Group 1</td>
<td>0.94±0.08</td>
<td>0.0031 (Sig)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>0.60±0.20</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Group 1</td>
<td>0.67±0.21</td>
<td>0.1289 (NS)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>0.94±0.34</td>
<td></td>
</tr>
<tr>
<td>BOP</td>
<td>Group 1</td>
<td>1.02±0.31</td>
<td>0.2140 (NS)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>0.79±0.29</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Group 1</td>
<td>1.88±0.54</td>
<td>0.7688 (NS)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>1.99±0.71</td>
<td></td>
</tr>
<tr>
<td>CAL</td>
<td>Group 1</td>
<td>2.73±1.12</td>
<td>0.6100 (NS)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>3.06±1.05</td>
<td></td>
</tr>
</tbody>
</table>

P<0.05 is considered significant. SD: Standard deviation, BOP: Bleeding on probing, PD: Probing depth, CAL: Clinical attachment level, Sig: Significance, NS: Nonsignificance, PI: Plaque index, GI: Gingival index.

Table 3: Intragroup comparison of Fasting blood sugar and Glycosylated haemoglobin at Baseline and after Treatment

<table>
<thead>
<tr>
<th>FBS mg/dl, Mean±SD</th>
<th>HbA1c mg/dl, Mean±SD</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>178.2±11.2</td>
<td>8.5±0.9</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td>150.0±0.9.8</td>
<td>7.3±0.6</td>
<td></td>
</tr>
<tr>
<td>Mean reduction</td>
<td>18.2±1.4</td>
<td>1.2±0.3</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>182.4±10.4</td>
<td>8.9±1.1</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td>130.2±8.8</td>
<td>6.7±0.5</td>
<td></td>
</tr>
<tr>
<td>Mean reduction</td>
<td>52.4±1.6</td>
<td>2.2±0.6</td>
<td></td>
</tr>
</tbody>
</table>

SD - Standard deviation FBS - Fasting blood sugar HbA1c - Glycosylated Haemoglobin. P<0.05 is considered significant.

Table 4: Intragroup comparison of Fasting blood sugar and Glycosylated haemoglobin at baseline and after treatment

<table>
<thead>
<tr>
<th>FBS</th>
<th>HbA1c</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Group 1</td>
<td>178.2</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>182.4</td>
</tr>
<tr>
<td>After</td>
<td>Group 1</td>
<td>150.0</td>
</tr>
<tr>
<td>Treatment</td>
<td>Group 2</td>
<td>130.0</td>
</tr>
</tbody>
</table>

SD - Standard deviation FBS - Fasting blood sugar HbA1c - Glycosylated Haemoglobin. P<0.05 is considered significant.

cross-sectional studies have shown the elevated level of IL-6 with features of insulin resistance syndrome an overt type-2 DM.[23]

In our study, there was a statistical significance in all the clinical parameters on intraintragroup comparison both in Group 1 and 2 patients. Nonsurgical periodontal treatment helps to reduce the microbial load, thereby showing improvement in glycemic control. Diabetes and periodontal disease are two chronic diseases that have long been considered to be biologically linked. The patients with DM had significantly more clinical attachment loss than nondiabetic patients. Cross-sectional studies done by Grossi et al. have shown that diabetic patients were twice as likely as nondiabetic patients to have clinical attachment loss.[23] In another cross-sectional study done by Bridges et al., it was found that DM affected all periodontal parameters, including bleeding scores, PD, and loss of attachment.[24] Fenugreek seeds exert hypoglycemic effects by stimulating glucose-dependent insulin secretion from pancreatic beta cells, as well as by inhibiting the activities of alpha-amylase and sucrase, two intestinal enzymes involved in carbohydrate metabolism. Therefore, a considerable improvement in glycemic control helps to improve the periodontal parameters significantly. The improvement in all the clinical parameters in this study was similar to a study done by Rodrigues et al.[25]
In our study, when intragroup comparison was done, there were statistically significant changes seen in both the groups for FBS and for HbA1c in Group 2 patients alone. Similarly, when intergroup comparison was done for FBS and HbA1c individually, there was statistical significance observed only for FBS after treatment. Periodontal treatment that reduces periodontal inflammation may help to restore insulin sensitivity, thereby improving glycemic control.\textsuperscript{[26]} In our study as an adjunct to SRP, metformin was given to Group 1 patients and fenugreek was given along with metformin to Group 2 patients. In many diabetic patients, blood glucose levels are not properly controlled by bonafide antidiabetic medicines and malnourished individuals take suboptimal doses of the drug to prevent hypoglycemic episodes. As fenugreek is commonly used as a condiment in India, the beneficiary effect of fenugreek in controlling blood sugar and overall cholesterol levels would have a considerable practical implication. The biochemical benefits of the fibers present in fenugreek facilitate insulin secretion as a result of 4-hydroxyisoleucine which helps to lowering the rate of glucose absorption in the intestines, thus controlling the blood sugar levels.\textsuperscript{[15]} Besides 4-hydroxyisoleucine, arginine, and tryptophan are the other amino acids having antidiabetic and hypoglycemic effect. In addition to this, many trace elements, which are the components of Trigonella, have been found to possess antidiabetic effects. Since fenugreek seeds are a source of protein, they can replace pulses in the diet of a diabetic patient. About 25–50 g fenugreek in the diet of diabetic patients (taken daily) can be an effective supportive therapy in the management of diabetes.\textsuperscript{[27]}

In our study, there was a statistically significant reduction in blood glucose, as evidenced by a reduction in the FBS and HbA1c levels compared to baseline values after administering fenugreek along with metformin. The bioactive compounds with respect to diabetic conditions include the galactomannan-rich soluble fiber fraction of fenugreek which may be responsible for the antidiabetic activity of the seeds.\textsuperscript{[28]} Fenugreek seeds contain 25% fiber that can slow the rate of postprandial glucose absorption. This may be a secondary mechanism for its hypoglycemic effect.\textsuperscript{[29]} Animal studies done by Mishkinsky \textit{et al.} and Madar and Ribes \textit{et al.} \textsuperscript{[30-32]} showed that fenugreek seeds reduce fasting and 2 h postprandial glucose levels. In another human study done by Sharma and Al Hobori and Raman,\textsuperscript{[33,34]} the hypoglycemic effect of fenugreek seeds in both type 1 and type 2 DM patients were found to be significant.

In our study when intragroup comparison was done to see the IL-6 level, there was a statistical significant reduction seen in both the groups. Similarly, when intergroup comparison was done, there was no significance observed in both groups. In a study conducted by D’Aiuto \textit{et al.}, they found a significant reductions in CRP and IL-6 serum levels, along with improvement in all clinical periodontal parameters with nonsurgical periodontal therapy.\textsuperscript{[35]} Similar studies were conducted by Tonetti \textit{et al.} where they suggested that CRP and other markers might not adequately reflect the relevant inflammatory pathways or that the long-term improvements were independent of the systemic inflammatory response.\textsuperscript{[36]} Yamazaki \textit{et al.} reported that there was no statistically significant difference in IL-6 and high sensitivity CRP before and after therapy.\textsuperscript{[37]} The lack of statistical significance in this study on the intergroup comparison may reflect the various contributions made by periodontal disease to the total burden of inflammation in different patients and the limited duration of the study. Nonsurgical periodontal treatment not only reduces clinically evident inflammation but also has been associated in decreasing proinflammatory cytokines and glycated hemoglobin levels indicating that periodontal diseases have systemic effects extending beyond the local periodontal environment.

In this study, the use of fenugreek seeds in uncontrolled diabetic patients could have added the additional benefit of antidiabetic effect observed in this study, which consequently helps to reduce the circulating inflammatory cytokine systemically. The limitation of this study is the short-term benefit observed with nonsurgical therapy with the help of fenugreek seeds as an adjuvant to regular antidiabetic medicines. Further studies are needed to assess the effect of fenugreek on long-term basis with regular follow-up.

\section*{Conclusion}
Severe generalized periodontitis seems to contribute to systemic inflammation. Nonsurgical periodontal therapy can cause reductions in the serum levels of proinflammatory cytokines such as IL-6 and glycated hemoglobin levels. Fenugreek used in this study as an adjuvant to nonsurgical therapy might have added additional benefit in reducing the glycemic status in these uncontrolled diabetic patients which was evident by the reduction in FBS and HbA1c values observed in this study. There was also a significant reduction in the PI in this study, which could be due to the direct effect of fenugreek on FBS level. Although the current therapies used to manage periodontitis may be adequate to simultaneously manage systemic sequelae, no periodontal treatment protocols are available that are specifically designed to improve systemic status. Further studies in this regard could lead to the emergence of novel therapeutic measures.

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\section*{Conflicts of interest}
There are no conflicts of interest.

\section*{References}


