S. Gopalakrishnan et al /J. Pharm. Sci. & Res. Vol. 12(6), 2020, 829-835

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Effects of Trigonella Foenum Gel as an Adjunct to SRP on GCF Resistin in Periodontitis Subjects with Type 2 Diabetes Mellitus

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Abstract:

Aim: The aim of the study was to evaluate the effect of trigonella foenum gel as an adjunct to nonsurgical periodontal therapy on GCF levels of Resistin in Periodontitis patients with Type 2 Diabetes Mellitus.

Materials and methods: 120 Periodontitis patients with Diabetes Mellitus participated in this study and were randomly divided into two groups [Group 1: 60 periodontitis patients with Type 2 DM treated with SRP alone, Group 2: 60 periodontitis patients with Type 2 DM treated with SRP along with trigonella foenum gel]**.** Plaque Index, Gingival Index, Sulcus Bleeding Index, PPD, CAL, and FBS were recorded at the baseline and one month after treatment. GCF & blood samples were taken for analysis of Resistin and FBS respectively.

Results: Intragroup comparison for the clinical parameters showed statistically significant reduction in both the Groups ($p<0.0001$). Intergroup comparison for clinical parameters showed statistical significance seen after 30days except for Bleeding on Probing (p- 0.1200). Intragroup comparison of FBS ($p<0.001$and $p<0.0006$) and GCF Resistin ($p<0.0013$ and $p<0.0021$) showed significance reduction in both the groups. On Intergroup comparison of FBS and GCF resistin, significant reduction was seen in Group 2 after one month ($p<0.0020$ and $p<0.0034$) respectively.

Conclusion: Trigonella foenum gel could be used as an adjunct to nonsurgical therapy in Periodontitis patients with Type 2 Diabetes Mellitus.

Keywords: Periodontitis, GCF Resistin, SRP, Trigonella Foenum gel, Type 2 Diabetes Mellitus.

Key findings of the study: Fenugreek causes significant improvement in clinical parameters due to its antioxidant and anti-inflammatory properties. There is significant reduction in GCF Resistin levels in Group 2 patients after application of fenugreek gel as an adjuvant to SRP.

INTRODUCTION:

Periodontitis is a multifactorial disease of tooth supporting structures. Though initiation is dependent on the host response to microbial challenge, the progression of the disease is mainly by the local and systemic factors. [1] Diabetes Mellitus has long been recognized as one of the pandemic cause of morbidity and mortality. There is an extensive literature suggesting a Two -Way relationship between Diabetes and Periodontitis, where, one disease affects the other as both are associated with exaggerated inflammatory response. Numerous mechanisms have been elucidated to explain the impact of Diabetes Mellitus on periodontium while inflammation is the primary linking factor for both the diseases. Periodontitis, being described as the sixth complication of Diabetes Mellitus has been directly correlated with the level of glycemic control. [2]

Recently, the role of adipose tissue is linked to many endocrinal activity rather than fat production and storage. The adipokine from the adipose tissue are considered as adipocytokine that act as pro inflammatory cytokines. Many such adipokines have been discovered to be associated with systemic diseases. One such adipokine is Resistin, that derived its name from an original observation inducing insulin resistance in mice. Resistin was thought to be produced only by adipocytes, but studies have shown its origin from hypothalamus, pituitary, adrenal glands, pancreas, gastrointestinal tract, myocytes, spleen, plasma and immune cells like PMNs, monocytes and macrophages.[3] Resistin is a member of a family of tissue-specific signaling molecules called as resistin-like molecules. Since the discovery of resistin in 2001 as a 'link' between obesity and Diabetes, researchers have increasingly focused on the pleiotropic role of

resistin and its biological functions. Further researches have linked resistin to other physiological systems such as inflammation and energy homeostasis. Human resistin also acts as a pro-inflammatory molecule and stimulates the synthesis and secretion of pro-inflammatory cytokines like Tumor Necrosis Factor (TNF-α), Interleukin-6 (IL-6), IL-12, and Monocyte Chemoattractant Protein (MCP) -1. [4] A three-way relationship has also been established between Diabetes, obesity and periodontitis. Previous researches highlighted the gradual rise of resistin levels with periodontal disease activity and a reduction in its level after periodontal therapy. Resistin levels were found increased in inflammatory conditions like rheumatoid arthritis, chronic kidney diseases, atherosclerosis, and coronary heart diseases. Thus resistin would be one of the molecular link connecting periodontitis with many systemic diseases.[5] Human resistin is found to compete with lipopolysaccharide for the binding to Toll-Like Receptor-4, which could mediate some of its well-known pro- inflammatory effects.[6] Resistin antagonizes insulin action, and it is down-regulated by rosiglitazone and peroxisome proliferator –activated receptor agonists.[7, 8]

Nonsurgical Periodontal Therapy is the cornerstone of periodontal therapy and the first recommended approach to the control of periodontal infections. The main objective of SRP is to recover gingival health by completely eliminating components that are responsible for the gingival inflammation in the oral environment. Mechanical debridement induced enhanced change in the composition of the subgingival microflora [9]. When SRP is complemented with local or systemic antibiotics, its effect is enhanced. Many Local drug delivery agents have been tried and found to be successful as an adjunct to SRP. Due to the side effects of long-term systemic antibiotics, many Local drug delivery agents have been tried and found to be successful as an adjunct to SRP. Recently herbal alternatives have been tried as LDD due to its complex structure, lack of resistance and no side effects. One such herbal alternative is fenugreek.

Trigonella Foenum also known as Fenugreek seeds, are ancient herbal medicine with anti- diabetic, anti-inflammatory, antioxidant, hypocholestrolemic and mild antimicrobial properties. Fenugreek seeds have been used for the treatment of Diabetes Mellitus (DM) in many parts of the world, including India. [10] The seeds of fenugreek contain lysine and L-tryptophan rich proteins, mucilaginous fiber and other rare chemical constituents such as saponins, coumarin, fenugreekine, nicotinic acid, sapogenins, phytic acid, scopoletin and trigonelline, which are thought to account for many of its presumed therapeutic effects may inhibit cholesterol absorption and thought to help lower sugar levers by Billaud, Sauvaire et al and Sauvaire et al.[11,12] 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. Hypoglycemic properties of fenugreek are mainly due to galactomannan, 4‑hydroxyisoleucine (4‑OH‑Ile). 4‑hydroxyisoleucine is a natural nonprotienogenic aminoacid possessing noninsulinotropic biologic activity causing increased glucose induced release of insulin through a direct effect on the isolated islets of Langerhans.[13] In humans, fenugreek seed is found to 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. [14] In our previous study, fenugreek seed powder along with metformin was helpful in reducing blood glucose level and clinical parameters in periodontitis patients with Diabetes Mellitus. [15] Since diabetic patients have increased adipocytokine level, this study was carried out to compare the effect of Trigonella Foenum Gel as an adjunct to SRP on GCF Resistin in Periodontitis subjects with Type 2 Diabetes Mellitus

MATERIALS AND METHODS:

120 patients were randomly chosen from a total of 150 out-patients in the Department of Periodontics, Thai Moogambigai Dental College and Hospital, Mogappair, Chennai. The study protocol was approved by the ethical committee of Dr. M.G.R University, Maduravoyal, Chennai, in accordance with the Declaration of Helsinki, as revised in 2003. This study consisted of 120 participants who were divided into two groups as follows:

Group 1: 60 Periodontitis patients with Type 2 DM treated with SRP alone.

Group 2: 60 Periodontitis patients with Type 2 DM treated with SRP& fenugreek gel.

Informed consent was obtained from all patients. All the patients involved in this study had controlled DM that was confirmed based on the glycosylated hemoglobin (HbA1c) (values >7 mg/dl) levels taken at baseline for every individual. The history of diabetic patients selected for the study was >5 years. Clinical parameters were recorded; GCF and blood samples were obtained from the participants of both groups at baseline and one month after nonsurgical periodontal therapy. The duration of the study to procure 120 patients was two months.

Inclusion criteria

The inclusion criteria in the study were patients who were suffering from Periodontitis with controlled Type 2 DM. They should have at least 30% of the sites with Clinical Attachment Level (CAL) ≥4 mm, Pocket Depth (PD) of ≥5 mm, and Bleeding on Probing (BOP) more than 10 sites.

Exclusion criteria

Patients who undergone periodontal therapy during past 6 months, those with history of antibiotic intake, pregnant woman, lactating mothers, obese, smokers, liver disease, insulin therapy and alcohol consumption.

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: Plaque Index (PI) (Silness and Loe 1964), Gingival Index (PI) (Loe and Silness

1963), Sulcus Bleeding Index (Muhlemann and Son 1971), Periodontal Pocket Depth (PPD) and Clinical Attachment Level (CAL) were evaluated at baseline and one month after treatment. Blood samples were collected after a minimum of 10 hours of overnight fasting for all individuals at baseline and one month after treatment. GCF samples were taken at baseline and one month after treatment. After recording the parameters, patients underwent full mouth non-surgical periodontal treatment under local anesthesia in two consequent visits within 24 hours. Group 1 patients underwent SRP alone while Group 2 patients underwent SRP and received Trigonella foneum gel.

Fenugreek Gel Preparation:

Trigonella foneum [Fenugreek] seeds were procured from IMPCOPS Ltd., (Chennai, India). The seeds were air dried for 7 days at room temperature. The dried seeds were weighed and grounded using high speed grinder [14]. This powder was subjected to ethanolic soxhlet extraction for 48 hours and then dried under waterbath to obtain the concentrated extract. The extract was utilized for gel preparation. Extract was mixed with poloxamer 405, distilled water and methyl paraben. In this gel, poloxamer 405 is the polymer, methyl paraben is preservative and distilled water was used to adjust the consistency. The final gel was stored in refrigerator until use. The gel has an advantage of becoming liquid at lower temperature and converting to gel. This process of converting to liquid and gel form and back to liquid form is called reversible hydrocolloid property. This is illustrated in [Fig I]

Fenugreek Gel Application:

After thorough SRP, patients in Group 2 received fenugreek gel. The deepest probing pocket in each quadrant was selected and Fenugreek gel was administered into the periodontal pocket with syringe with a blunt cannula. Excess gel is allowed to flow in the interproximal area to check for the hydrocolloidal effect and later wiped off. [Fig II]

Sample collection

Venous blood samples were collected in the morning after an overnight fast of 12 hours for Fasting Blood Sugar (FBS) and HbA1c analysis. Fasting blood glucose level was measured using the glucose oxidase peroxidase method.[16] The HbA1c concentration was measured using Column method.[17] HbA1c test was performed for all the participants to confirm their diabetic status. GCF samples were collected from deepest pocket using micropipette (extrasulcular method) at baseline and one month after treatment [Fig III]. GCF samples were analyzed for resistin level using a highly sensitive sandwich ELISA using human Resistin ELISA test kit (Korain Biotech, Shanghai, China) [Fig IV].

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. Intergroup comparison of mean reduction from baseline for all the parameters (PI, GI, BOP, PPD, CAL, FBS, and GCF Resistin) was analyzed using the unpaired t test.

RESULTS

Intragroup comparison showed statistical significance in both the groups for all the clinical parameters (Table 1). Intergroup comparison showed statistical significance for all the parameters except Bleeding on probing (P< 0.1200) (Table 2).Intragroup comparison was done for FBS, at baseline, and after SRP, there was a statistical significance observed (P <0.001 and P < 0.006) (Table 3). Intergroup comparison was done for FBS, at baseline, and after SRP, there was a statistical significance observed (P < 0.0020) (Table 4). Intragroup comparison was done for GCF resistin, at baseline, and after SRP, there was a statistical significance observed (P <0.0013 and P < 0.0031) (Table 5). Similarly, when intergroup comparison was done for GCF resistin after treatment, there was statistical significance seen in Group 2 patients (P <0.0034) (Table 6).

Table 1: Intragroup comparison of clinical parameters using paired t test:

	Plaque Index Mean ± SD	Gingival Index Mean ± SD	Sulcus Bleeding Index Mean ± SD	Pocket Depth Mean ± SD	Clinical attachment level Mean ± SD
Group I		2.43±0.62			
Baseline	2.09±0.05		2.16±0.05	3.80±0.09	4.14±0.02
After Treatment	1.09±0.04	0.69±0.26	1.04±0.02	2.42±0.04	3.05±0.01
P value	0.0012	0.0016	0.0001	0.0013	0.0001
Group II					
Baseline	2.11±0.02	2.66±0.37	2.18±0.05	3.85±0.04	4.17±0.24
After Treatment	0.92±0.08	0.67±0.21	1.01±0.03	2.34±0.05	2.71±0.01
P value	0.0001	0.0001	0.0001	0.0001	0.0001

SD –Standard Deviation

P<0.05 is considered significant

Table 2: Intergroup comparison of parameters after Treatment using independent t test:

Parameters	Groups	After Treatment	P value
Plaque index	Group 1 Group 2	1.09±0.04 0.92±0.08	0.0006
Gingival Index	Group 1 Group 2	0.69±0.26 0.67±0.21	0.0001
Sulcus Bleeding Index	Group 1 Group 2	1.04±0.02 1.01±0.03	0.1200
Pocket Depth	Group 1 Group 2	2.42±0.04 2.34±0.05	0.0029
Clinical attachment level	Group 1 Group 2	3.05±0.01 2.71±0.01	0.0001

P<0.05 is considered significant

Table 3: Intragroup comparison of Glycemic status using FBS Values

Groups	HbA1C	FBS	P Value
Group I			
Baseline	Baseline 6.5± 1.4	151.29±3.61	0.001
After treatment		131.3±3.95	
Group II			
Baseline	Baseline 6.7± 1.2	151.21± 4.53	0.0006
After treatment		122.1± 4.43	

FBS-Fasting blood sugar, HbA1c- Glycosylated haemoglobin
P<0.05 is considered significant

Table 4: Intergroup comparison of Glycemic status after treatment using FBS Values

Parameters	Groups	After Treatment	P value
FBS	Group 1 Group 2	131.3±3.95 122.1± 4.43	0.0020

FBS-Fasting blood sugar
P<0.05 is considered significant

Table 5: Intragroup comparison of Resistin using paired t test:

Groups	Baseline	After Treatment	P value
Group I	197.7±6.75	117.49±6.19	0.0013
Group II	199.85±4.81	107.74±6.10	0.0021

P<0.05 is considered significant

Table 6: Intergroup comparison of Resistin using independent t test:

	Group I	Group II	P value
Baseline	197.7±6.75	199.85±4.81	0.4611
After Treatment	117.49±6.19	107.74±6.10	0.0034

P<0.05 is considered significant

Figure 1 – Reverse hydrocolloid effect of fenugreek gel

Figure II – fenugreek gel placed

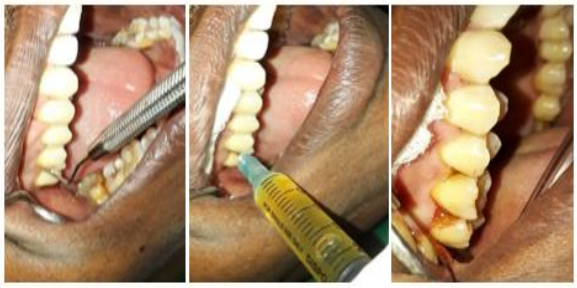


Figure III- GCF collection

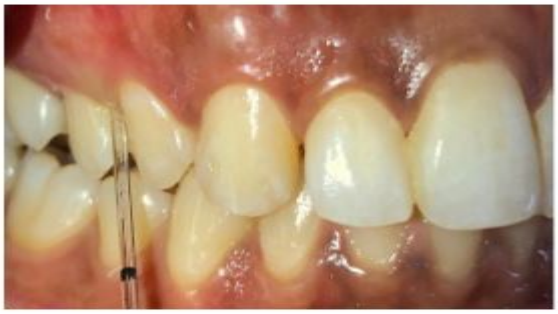
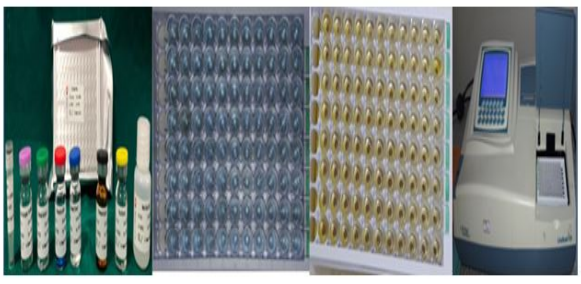


Figure IV – ELISA processing



DISCUSSION

Periodontitis is considered as the sixth complication of diabetes, and there has been a bidirectional relationship established between diabetes and periodontitis, wherein one can influence the other [18]. Chronic subclinical inflammation in periodontitis has been shown to decrease the insulin sensitivity. Currently the role of adipose tissue-derived substances "adipokines" in immune- inflammatory responses has been appreciated. Various pro inflammatory cytokines studied have shown to play an important role in the periodontal pathogenesis and diabetes. One such newly recognized group of cytokines is adipokines. Adipokines like adiponectin, resistin are postulated to act through their effects on insulin sensitivity and recent evidence suggests an important role of these adipokines in the inflammatory process.[19] Levels of resistin are found to be increased in periodontitis, and resistin plays an important role in inducing insulin resistance, thus increasing the risk for Type 2 Diabetes.[20] Resistin has elevated levels in destructive periodontal diseases suggesting that it primarily functions during progression of periodontal diseases.[21] Resistin could potentially play in the etio-pathogenesis of both local and systemic inflammatory conditions as evidenced in Periodontitis, Obesity and DM, thereby translating into its utility as a potential marker of inflammation in periodontal disease, Obesity and T2DM. The reason for using Trigonella foneum [Fenugreek] as gel is due to its role in insulin regulation, anti inflammatory and mild anti microbial properties. The effect of fenugreek powder along with Metformin as an adjunct to SRP in Periodontitis subjects with uncontrolledT2DM was proven in our earlier study [15]. This gave rise to an idea of utilizing fenugreek as LDD in Periodontitis subjects. The advantage of this gel is its reversible hydrocolloid effect. The gel is in liquid form when refrigerated and converts to solid gel form when placed at room temperature due to the polymer Poloxamer 405. In periodontitis, the temperature inside periodontal pocket is elevated than normal which makes the semi-liquid consistency to get readily converted to gel form without dissipation from the periodontal pocket [Fig 2]

In our study, Plaque Index was taken to assess the ability of oral hygiene maintenance after periodontal therapy by the patient. On Intragroup comparison, there was a statistical significance in all the clinical parameters in both the Groups. Nonsurgical periodontal treatment helps to reduce the microbial load, thereby showing improvement in glycemic control. In a 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 [22]. Intergroup comparison in our study showed significance for all parameters except for Sulcus Bleeding Index. This could be due to the Fenugreek gel which exerts anti-inflammatory and mild antimicrobial property. Fenugreek has also antioxidant property which helps in scavenging free radicals released from the inflammatory cells. This property would have enhanced the application of fenugreek gel in the infected site to reduce the inflammation and also helps in significant reduction in clinical parameters. The improvement in all the clinical parameters in this study was similar to a study done by Rodrigues et al [23]. In our previous study, there was an improvement in plaque index in diabetic patients after consumption of fenugreek powder. [15] Nonsurgical periodontal treatment not only reduces inflammation but also aids in decreasing adipocytokines and blood glucose levels supporting the fact that periodontitis have systemic influence.

In our study, there was a statistically significant reduction in blood glucose, as evidenced by a reduction in the FBS after nonsurgical periodontal therapy compared to baseline values. On Intergroup comparison, there was significant reduction in FBS level in Group 2 where fenugreek gel was given as an adjunct to SRP. The anti-diabetic activity could be due to the bioactive compounds like galactomannan‐rich soluble fiber and 4-hydroxyisoleucine (4‐OH‐Ile) present in fenugreek [24]. 4‐OH‐Ile is a natural non- proteinogenic amino acid with non- insulinotropic activity that has a direct effect on islets of Langerhans. Earlier studies have shown that fenugreek increased the number of insulin receptors and reduced the area under the plasma glucose curve [25]. Glucose dependent insulin from pancreatic beta cells is stimulated by the hypoglycemic effects of fenugreek. Fiber content in Fenugreek decreases the glucose absorption rate when taken orally [26]. In our previous study it was shown that fenugreek powder can be used as an adjunctive to SRP to control the glycemic status and serum lipid levels in uncontrolled NIDDM patients. [27] In this study the reduction in FBS levels in Group 2 was due to the improvement in clinical parameters which indirectly regulates the systemic glycemic levels and local application of fenugreek gel could have contributed as an additional benefit to control the local inflammation due to its anti inflammatory property.

In our study when intragroup comparison was done to see GCF Resistin level, there was a statistical significant reduction seen in both the groups. While intergroup comparison showed significant difference in Group 2. The result was in accordance with the study done by Devanoorkar et al.[28] The fenugreek gel used in the study could have enhanced the effect of SRP in Group 2 patients. The effects of galactomannan, 4‐hydroxyisoleucine in fenugreek seed has indirectly impaired the production of resistin. Periodontitis, being a disease of multiple origins, is characterized by stimulation of host immune- inflammatory system in response to microbial deposits and their endotoxins produced. Host immune-inflammatory system, in an attempt to clear the infections, causes the infiltration of periodontal tissues by various immune-inflammatory cells such as PMNs, monocytes, and macrophages.[29,30] Cytokines such as TNF-α, CRP, interleukins, prostaglandins, and resistin not only causes periodontal tissue destruction but also exert certain distant systemic effects such as increased risk for atherosclerosis, PTLBW, and increased insulin resistance. Furugen et al. investigated the levels of adipokines such as resistin, adiponectin, TNF- α, and IL-6 in chronic periodontitis subjects in elderly Japanese individuals and reported that serum resistin levels were higher in

periodontitis patients compared with the healthy subjects.[31] Resistin is a recently identified adipocyte-derived hormone that has been shown to play a substantial role in the development of insulin resistance.[32] The role of resistin in the links between obesity, insulin resistance, and diabetes was hypothesized in rodents. Nonsurgical periodontal therapy helps to reduce the inflammatory cytokines. In this study, the use of fenugreek gel in diabetic patients with periodontitis could have added the extra benefit of anti-diabetic and antioxidant effect, which thereby helps to reduce the resistin levels in GCF. The ethanolic extract of fenugreek has shown to exhibit excellent anti inflammatory property in rat model [33]. To the best of author's knowledge, this is the first study attempted to prove the efficacy of fenugreek gel on GCF resistin levels in Periodontitis patients with T2DM.

LIMITATIONS

The limitations of this study are the short term benefit observed with single time application of fenugreek gel as an adjunct to nonsurgical periodontal therapy. The effect of fenugreek on resistin is not proven systemically. Fenugreek effect on serum resistin should be evaluated to prove its efficacy. The reduction in glycemic levels of the patients after treatment were only confirmed with FBS and HbA1c levels were not taken after treatment, which is a better predictor of glycemic status. Further studies are required to assess the effect of multiple time application of fenugreek gel on long term basis with regular follow-up to substantiate the result of our study.

CONCLUSION

Periodontitis and Diabetes Mellitus share a Bi-directional relationship. Nonsurgical periodontal therapy can not only reduce inflammatory components, but is proven to reduce blood glucose levels. Fenugreek gel along with SRP might have provided additional benefit on glycemic status by not only reducing FBS levels, but also improving periodontal condition. Hence Trigonella foneum gel could be used as an adjunct to SRP in Periodontitis patients with Type 2 Diabetes Mellitus. This study has paved way for future studies with long duration to improve therapeutic measures.

List of each author's contribution:

Dr. S. Gopalakrishnan– Conceptulisation, sample collection, analysis of data, drafting the manuscript.

Dr. Ramakrishnan- Conceptulisation, drafting the manuscript, critical revision

Dr. Gomathi.G.D -Drafting the manuscript, sample collection, analysis of data

Dr. Gnanasagar. W.R- sample collection, analysis of data

Dr. G. Kanimozhi- sample collection, analysis of data, critical revision

REFERENCES

1. Kornman KS. Mapping the pathogenesis of periodontitis: A new look. *Journal of Periodontology* 2008; 79:1560-1568.
2. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993; 16:329-334.
3. Pischon N, Heng N, Bernimoul in JP, Kleber BM, Willich SN &Pischon T. Obesity, inflammation, and periodontal disease. *Journal of Dental Research* 2007;86:400–409.
4. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S et al.Human resistin stimulates the pro-inflammatory cytokines TNF alpha and IL-12 in macrophages by NF-kappa B-dependent pathway. *Biochemical and Biophysical Research Communications* 2005;334:1092-1101.
5. S. S. Pang and Y. Y. Le, "Role of resistin in inflammation and inflammation-related diseases," *Cellular & Molecular Immunology*.2006; 3(1): 29–34.
6. Ebersole JL, Holt SC, Hansard R, Novak MJ, Microbiologic and immunologic characteristics of periodontal disease in Hispanic Americans with type 2 diabetes. *J Periodontol*2008; 79: 637–646.
7. T.Liu,H.A.Baek,H.Yuetal.,"FIZZ2/RELM-β induction and role in pulmonary fibrosis,"*The Journal of Immunology*. 2011; 187(1):450–461
8. B. Gerstmayer, D. K ¨ usters, S. Gebel et al., "Identification of RELMγ,anovelresistin-likemoleculewithadistinctexpression pattern,"*Genomics*,2003; 81,(6): 588–595.
9. Nadkarni KM. Trigonellafoenumgraecum. *Indian Mater Med* 1993; 2: 1240-1249.
10. Neerja A, Rajyalaxmi P. Hypoglycemic effect of processed fenugreek seeds in humans. *J Food SciTechnol* 1996; 33: 427-430.
11. C. Billaud, Sciences-des-ailments. 21 (2001) 3. 12.
12. Y. Sauvaire, G. Ribes, J.C. Baccou and M. M. Loubatieres-Mariani, Lipids Mar. 26 (1991)191
13. Ajabnoor MA, Tilmisany AK. Effect of Trigonellafoenumgraceum on blood glucose levels in normal and alloxan-diabetic mice. *J Ethnopharmacol* 1988; 22: 45-49.
14. Amin R, Abdul-Ghani AS, Suleiman MS. Effect of Trigonellafoenumgraceum intestinal absorption. *Diabetes* 1987; 36: 21-26.
15. Gopalakrishnan Sundaram, Ramakrishnan Theagarajan, Kanimozhi Gopalakrishnan, Gnanasagar Ramesh Babu, Gomathi Dhakshina Murthy. Effect of Fenugreek Consumption with Metformin Treatment in Improving Plaque Index in Diabetic Patients. *Journal of Natural Science, Biology and Medicine*2020; 11(1):55- 60.
16. Ambade VN, Sharma YV, Somani BL. Methods for estimation of blood glucose: A comparative evaluation. *Med J Armed Forces India* 1998; 54: 131-139.
17. Jaynes PK, Willis MC, Chou PP. Evaluation of a mini-column chromatographic procedure for the measurement of HbA1c. *ClinBiochem 1985*; 18: 32-36.
18. G.W.Taylor,"Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective,"*Annals of Periodontology*. 2001;61(1):99–112.
19. Pang S & Le Y.Role of Resistin in Inflammation and Inflammation-Related Diseases. *Molecular Immunology* 2006; 3(1):29-34
20. F.Nishimura,Y.Iwamoto,J.Mineshiba,A.Shimizu,Y.Soga,& Y. Murayama, "Periodontal disease and diabetes mellitus: the role of tumor necrosis factor- α in a 2-way relationship,"*Journal of Periodontology* 2003; 74: 197–102,
21. Furugen R, Hayashida H, Kitamura M & Saito T.Relationship between adipokines and periodontitis. *Japanese Dental Science Review* 2010;46(2):159–164.
22. Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR. Periodontal status of diabetic and nondiabetic men: Effects of smoking, glycemic control, and socioeconomic factors. *J Periodontol* 1996;67:1185-1192.
23. Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003;74:1361-1367.
24. Rashmi Y, Rahul K. Study of phytochemical constituents and pharmacological actions of Trigonellafoenumgraecum: A review. *Int J Pharm Technol* 2011; 3:1022- 1028.
25. Raghuram TC, Sharma RD, Sivakumar B, et al. Effect of fenugreek seeds on intravenous glucose disposition in non-insulin dependent diabetic patients. *Phytother Res1994*; 8:83-86.
26. Basch E, Ulbricht C, Kuo G, Szapary P, Smith M. Therapeutic applications of fenugreek. *Altern Med Rev* 2003;8:20-27.
27. Gopalakrishnan Sundaram, Theyagarajan Ramakrishnan, Harinath Parthasarathy, Manoj Raja, Samuel Raj. Fenugreek, diabetes, and periodontal disease: A cross‐link of sorts!Journal of Indian Society of Periodontology,2018; 22 (2): 122-126.

28. Devanoorkar A, Dwarakanath CD, Gundanavar G, Kathariya R & Patil SR. Evaluation of Serum Resistin Levels in Periodontal Health and Disease and Effects of NonSurgical Periodontal Therapy on Its Levels. *Disease Markers* 2012; 32 (5): 289–294.
29. C. Page, "The role of inflammatory mediators in the pathogenesis of periodontal disease," *Journal of Periodontal Research* 1991; 26 (3): 230–242.View at: Google Scholar
30. R. C. Page, "The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm," *Annals of Periodontology*, 1998; 3 (3): 108–120.
31. R.Furugen, H.Hayashida, N.Yamaguchi et al., "The relationship between periodontal condition and serum levels of resistin and adiponectin in elderly Japanese," *Journal of Periodontal Research*, 2008; 43 (5): 556–562.
32. C.M.Steppan & M.A.Lazar, "Resistin and obesity-associated insulin resistance," *Trends in Endocrinology and Metabolism*, 2002;13 (1): 18–23.
33. Kilambi Pundarikakshudu, Deepak H. Shah, Aashish H. Panchal and Gordhanbhai C. Bhavsar Anti-inflammatory activity of fenugreek (*Trigonella foenum-graecum* Linn) seed petroleum ether extract. Indian J Pharmacol. 2016 Jul-Aug; 48(4): 441–444