EGYPTIAN DENTAL JOURNAL
www.eda-egypt.org
VOL. 70, 3367:3377, OCTOBER, 2024
PRINT ISSN 0070-9484 • ONLINE ISSN 2090-2360
ORAL MEDICINE, X-RAY, ORAL BIOLOGY AND ORAL PATHOLOGY
Submit Date : 06-08-2024 • Accept Date : 26-09-2024 • Available online: 01-10-2024 • DOI : 10.21608/edj.2024.309230.3143

ASSESSMENT OF SEMAGLUTIDE THERAPY IN DIABETIC RATS WITH EXPERIMENTAL PERIODONTITIS

Soha M. Basha [*], Marwa M. Essawy [**], Nevien M. Ahmed [***] *and* Heba A. Shawky [****]

ABSTRACT

Background: Diabetes mellitus stands out as the most common systemic condition with a higher likelihood of developing and worsening periodontitis. Various pharmaceutical agents have been advocated to regulate glycemic levels in diabetic individuals.

Objective: To assess the effect of semaglutide on the periodontal tissue in diabetic rats with induced periodontitis.

Materials and Methods: Twenty-four male Albino Wistar rats weighing between 220 and 280 grams were recruited in the study. Eight rats were assigned randomly to three different study groups. These groups were as follows: Group A, the control group; Group B, which consisted of diabetic rats with induced periodontitis; and Group C, Semaglutide-treated rats. By the termination of the study period, rats were euthanized and were evaluated through microscopical examination and cytokines assessment.

Results: Diabetic group with induced periodontitis showed marked bone resorption with massive inflammatory infiltrate. Cytokine assessment displayed a noteworthy rise in the values compared to the control group. The semaglutide-treated group showed a substantial reduction in the cytokines level compared to the diabetic group with periodontitis which was manifested by improvement in the alveolar bone height and periodontium architecture.

Conclusion: Semaglutide showed potent effects in accomplishing glycemic control and improving the periodontal status in diabetic rats with induced periodontitis.

KEYWORDS: Diabetes, histological, interleukins, periodontitis, semaglutide

* Associate Professor of Oral Medicine, Diagnosis and Radiology, Department of Basic Dental Sciences, College of Dentistry, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia
** Oral Pathology Department, Faculty of Dentistry, Alexandria University, Alexandria, Egypt - Center of Excellence for Research in Regenerative Medicine and Applications (CERRMA), Faculty of Medicine, Alexandria University, Alexandria, Egypt
*** Department of Oral Biology-Biochemistry, Faculty of Dentistry, Pharos University in Alexandria, Egypt
**** Associate Professor of Periodontics, Department of Preventive Dental Sciences, College of Dentistry, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia

INTRODUCTION

Periodontitis is a chronic inflammation of the tissues that support teeth, and it is ranked as the second most common disease in the oral cavity. The defining features of periodontitis are the destruction of periodontal ligaments and the resorption of alveolar bone.[1] Dental biofilm initiates periodontitis by promoting host cells to generate pro-inflammatory cytokines. Therefore, the host immunoinflammatory response to microorganisms in the dental biofilm leads to periodontal destruction.[2]

The progression of periodontitis can be influenced by a variety of genetic, environmental, and/or systemic factors. Among these, diabetes mellitus (DM) stands out as the most common systemic condition linked to a higher likelihood of developing and exacerbating periodontal disease.[3] Diabetes mellitus (DM) is an endocrine disorder marked by elevated blood glucose levels brought on by insufficient amounts of the hormone insulin, which hinders the body's cells from effectively utilizing glucose. Insulin insufficiency arises mainly from two sources: either the pancreas is unable to produce enough insulin because the immune system targets the islet cells in the pancreas that produce insulin (T1DM) or the pancreas produces less insulin than is needed and the body becomes resistant to insulin (T2DM).[4] The concurrent epidemics of obesity and type 2 diabetes in different regions suggest that obesity is a significant risk factor for both prediabetes and T2DM. This can be explained by the fact that obesity leads to β-cell malfunction and insulin resistance.[5]

There has been extensive reporting on the reciprocal relationship between diabetes mellitus (DM) and periodontitis. The inflammatory mediators generated by periodontitis can lead to vascular inflammation, impact the glycemic balancing, and precipitate the emergence and advancement of diabetic complications.[6] Meanwhile, the persistent hyperglycemia state exacerbates clinical signs of periodontal disease such as clinical attachment loss, increased probing depth, and marginal bone loss. This occurs because the elevated glucose level speeds up the development and buildup of advanced glycation end-products (AGEs) in the periodontal tissues.[7] When AGEs and their receptors (RAGEs) interact, periodontal tissues experience an oxidative stress state that increases the synthesis of catabolic inflammatory cytokines.[8] Patient education, medical nutrition therapy, physical activity, and the prescription of oral hypoglycemic medications are all part of the general management of type 2 diabetes. Several anti-obesity pharmaceutical agents have been demonstrated to be helpful in obese diabetic patients, as obesity continues to be the strongest modifiable risk factor for type 2 diabetes.[9]

One of the commonly used classes of drugs administrated for the management of type 2 diabetes is called glucagon-like peptide-1 (GLP-1) agonists, sometimes referred to as GLP-1 receptor agonists, GLP-1 analogs, or incretin mimetics. GLP-1 agonists work by reducing blood glucose levels, which helps patients with the condition manage their metabolism. This class of medications includes, among others, exenatide, dulaglutide, liraglutide, and semaglutide.[10]

Semaglutide is the most recently approved agent of this drug class. It was initially authorized in the United States in 2017 to treat type 2 diabetes. Through a variety of cellular mechanisms, semaglutide efficiently lowers blood glucose levels and has shown strong antidiabetic effects. According to recent data, it may have advantages beyond glycemic control, such as helping obese people lose weight.[11]

The effect of different antidiabetic drugs on the periodontium was controversial. Metformin drug which belongs to the Biguanide class of antidiabetic medications demonstrated a beneficial effect on bone by inhibiting osteoclast formation and activity.[12] Similarly, Liraglutide, a GLP-1 receptor agonist considerably suppressed the periodontitis-related inflammatory cytokine expressions and alveolar bone resorption.[13] On the other hand, exenatide (GLP-1 receptor agonist) and sitagliptin (Dipeptidyl Peptidase IV inhibitor) are antidiabetic drugs approved by the Food and Drug Administration. Moraes et al. evaluated their effects on ligature-

induced periodontitis in rats. Results revealed that exenatide and sitagliptin drugs were ineffective in stabilizing or reducing alveolar bone loss and collagen degradation in rats.[14] To the authors' knowledge, prior research has not assessed the effect of semaglutide on periodontal tissue damaged by periodontitis. Thus, the current study is intended to assess the impact of semaglutide on the periodontal tissue in diabetic rats with induced periodontitis.

MATERIALS AND METHODS

The study involved twenty-four male Albino Wistar rats weighing between 220 and 280 grams on average. The research was conducted at the animal facility of Pharos University in Alexandria (PUA), and the procedure obtained authorization from the Unit of Research Ethics Approval Committee (UREAC) at PUA (02202402253191). All the rats were kept in regulated conditions with a temperature ranging from 24 to 26°C, a humidity level of 55 to 60%, and a 12-hour cycle of light to dark. They were also provided with unrestrained access to regular food and water. The experiment procedure complied with the rules and regulations specified in the Guide for the Care and Use of Laboratory Animals.[15]

Experimental Design

The animals spent one week in the animal housing facility to acclimate. Afterward, the rats were split at random into three groups of eight rats each. These groups were as follows: Group A, the control group; Group B, which consisted of diabetic rats with experimental periodontitis; and Group C, which included diabetic rats with experimental periodontitis receiving semaglutide therapy.

Sample size calculation

The sample size was estimated using OpenEpi sample size calculator. Based on previously reported reduction in the eroded bone area to 24.2 ± 5.0% with alendronate treatment of periodontitis compared to 93.4 ± 24.0% of the destructed untreated alveolar bone.[16] The size of each group was 7 rats, assuming 95% confidence interval and 80% study power. The number was increased to 8 rats to compensate any possible sample loss.

Induction of Diabetes

Diabetes was induced in the two experimental groups (Group B and Group C) through intraperitoneal injection of a 50mg/kg BW concentration of Streptozotocin (STZ)® (Sigma-Aldrich chemical company, Egypt) powder dissolved in a citrate buffer with a pH of 4.5 after a 12-hour fasting period.[17] The control group (Group A) was given an injection of citrate buffer into the peritoneum. To confirm diabetes, Fasting Blood Sugar (FBS) levels were checked three days after the administration of STZ, with rats having blood glucose levels exceeding 250mg/dl being identified as diabetic.

Treatment with Semaglutide

Starting on the fourth day after confirming diabetes, group C rats were given subcutaneous (SC) injections of semaglutide (Ozempic: Novo Nordisk, Bagsvaerd, Denmark) at a dose of 7μg/kg body weight, dissolved in a vehicle containing 44mM sodium phosphate dibasic, 70mM NaCl, and 0.007% Tween 20. The dose of semaglutide was increased to 70 μg/kg body weight over the following 10 days. Following this period, the 70 μg/kg body weight dose was sustained for 11 days until the study concluded.[18] Rats of groups A and B were injected with the vehicle SC daily.

Induction of Periodontitis

On the same day that the treatment application began, both groups B and C's rats were given anesthesia through an intraperitoneal injection of 80 mg/kg of Ketamine (Quetamina, Vetnil, São Paulo, Brazil) + 10 mg/kg of Xylazine (Calmium, São Paulo, Brazil). A 3.0 nylon suture thread (Polysuture, NP45330, São Paulo, Brazil) was used to tie around the mandibular right second molar, and the surgical knot was positioned on the vestibular side to induce periodontitis.[19] The ligatures remained in place for 21 days.

Measurement of FBS and body weight

The level of FBS was measured following overnight fasting before the STZ injection, three days after STZ injection, and then it was measured weekly in all animals from the three experimental groups. A sterile lancet was utilized to extract a single or double drop of blood from the tail capillaries to be used in the FBS experiment. The FBS levels were determined using the Glucometer (AccuChek Active Performa, Roche, Germany).[20] A portable electronic balance was used to measure the rats' weight once a week. After euthanasia, Serum Glucose level was measured using a commercial kit (Glucose Kit from Bio diagnostic, Giza, Egypt).

Animal Euthanasia and blood sample collection

At the conclusion of the study period, all animals were euthanized in accordance with the AVMA Guidelines for the Euthanasia of Animals using an overdose of anesthesia, which consisted of a combination of 100 mg/mL ketamine and 100 mg/mL xylazine.[21] Blood specimens were obtained through cardiac puncture, maintained at room temperature for coagulation, and subsequently spun for 15 minutes at 3000 rpm in a refrigerated centrifuge. The resulting serum layer was then transferred into labeled Eppendorf tubes and preserved at -20°C until the assay was conducted.

Assessment of serum cytokines

Serum from the blood of the experimental animals was used to analyze Tumor necrosis factor alpha (TNF-α), Interleukin-1 beta (IL-1β), Nuclear factor kappa B (NF-ϰB), and Interleukin 6 (IL-6). The analysis was performed using commercially available rat kits through Sandwich-ELISA (Enzyme Linked Immunosorbent Assay) Immunoassay. The ELISA kits used were from Elabscience-Biotechnology, based in Texas, USA. Standards or samples are meticulously added to the specified micro-ELISA strip plate wells and then mixed with the designated antibody. The Spectrophotometric measurement of absorbance or optical density (OD) is conducted at a wavelength of 450 nm for IL-1B, IL-6, TNF-α, and NF-ϰB. Using a microtiter Plate Reader, the readings were taken and the Optical Density value is directly proportional to their concentrations.

Microscopical evaluation

After animal sacrifice following the ethical guidelines, mandibles were dissected and 10% buffered formalin was fixed for 48 h. The ligated teeth were decalcified in 10% ethylenediaminetetraacetic acid (pH 7.8) for 8 weeks. Then, teeth-bearing areas were gradient-dehydrated and embedded in paraffin blocks. Serial 4–5 μm sections in a mesiodistal direction were histologically assessed using hematoxylin and eosin (H&E) staining. The examination was done blindly to the treatment plan using Olympus BX41 microscope. Digital photomicrographs were captured at ×10 and ×20 magnifications.[16]

Statistical analysis of the data

Data were entered into the computer and IBM SPSS software package version 20.0 (IBM Corp, Armonk, NY) was used for analysis. To confirm that the variable distribution was normal, the Shapiro-Wilk test was employed. ANOVA was utilized to compare the three groups under investigation, and the Post Hoc test (Tukey) was used for pairwise comparisons after that. At the 5% level, the findings were deemed significant.

RESULTS

Microscopical evaluation

Histological examination of the control group revealed the standard periodontium structure of thick alveolar bone and dense periodontal ligament fibers running in parallel bundles with minimum interstitial spaces and vasculature. In the diabetic group with induced periodontitis, the alveolar bone showed marked bone loss to downward to the level of the basal bone, with inflammatory cell infiltration in the fibrous tissue stroma and between the resorbed bone trabeculae. The periodontal ligament

showed pronounced disorganization of its bundles owing to the bone loss. An increased vasculature was a feature in the inflamed periodontium. The semaglutide-treated group showed alleviation of the inflammatory process, with restoration of the periodontium architecture. There was gain in the height of the interradicular alveolar bone, despite its irregular border. The periodontal ligament fibers restored the orientation and packing of their collagen bundles with diminished vasculature components that was pronounced in the untreated group (Fig. 1).

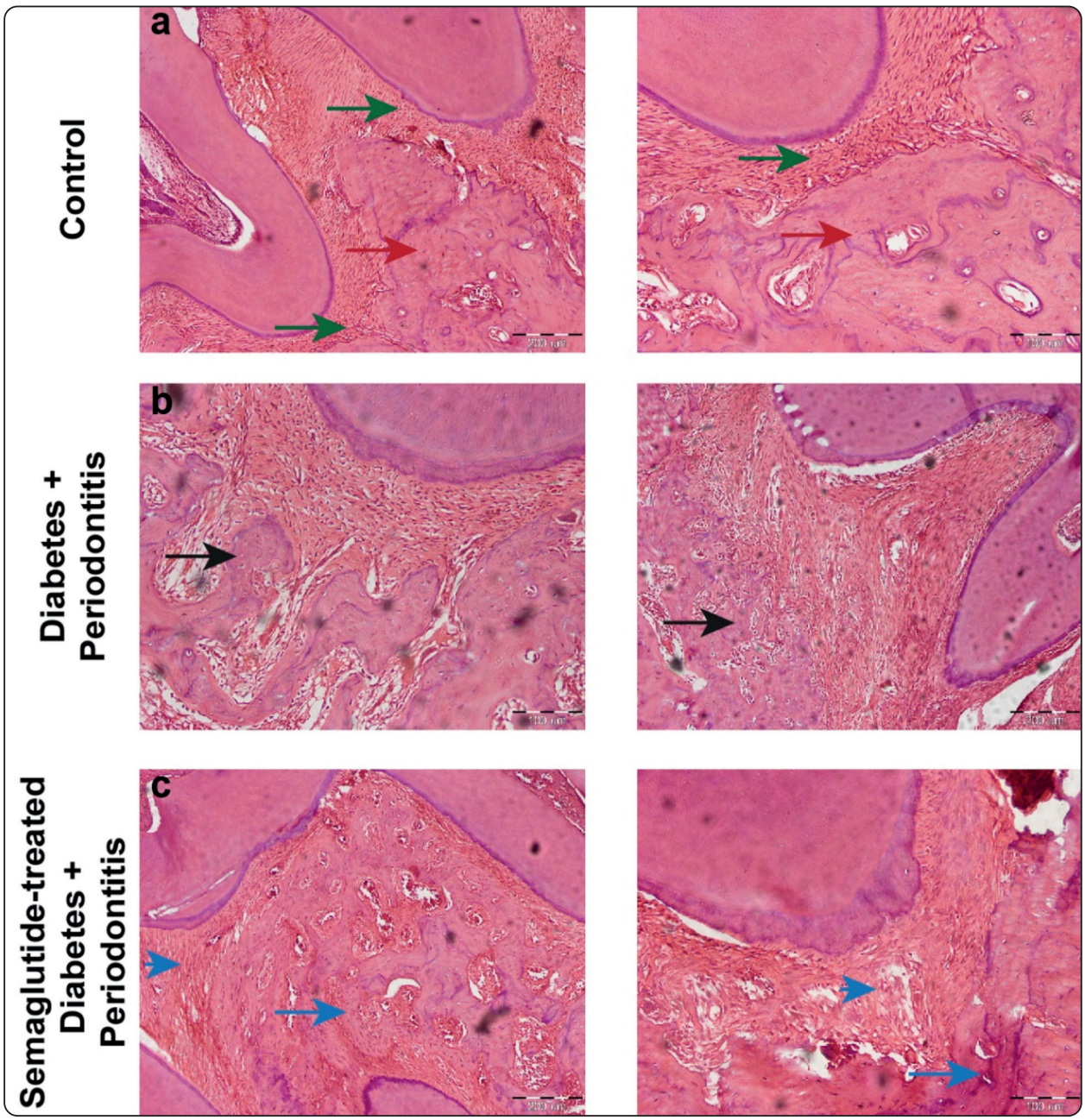

Fig. (1) Histological H&E-stained photomicrographs represent (a) the healthy status of the periodontium in the control group, with normal periodontal ligament fibers (green arrows) and well-formed alveolar bone (red arrows). (b) The resorbed alveolar bone in the diabetic animals with induced periodontitis to the level of the basal bone (black arrows). (c) The periodontium in the semaglutide-treated group attains normal fibrous (blue arrowheads) and bony architectures (blue arrows). Scale bar of 200 μm is of lens ×10, while 100 μm is of power ×20.

Body weight and Serum Glucose Level

Table (1) illustrates the results of body weight and glucose level. There was a significant ($p \leq 0.001$) decrease in body weight between the two experimental groups (diabetic group with induced periodontitis and the semaglutide-treated group) and the control group. However, when comparing the body weight of the semaglutide-treated group to the diabetic group with induced periodontitis, there was a significant ($p \leq 0.001$) drop.

Prior to the start of semaglutide administration, blood glucose levels in both experimental groups were found to be significantly ($p < 0.001$) higher than those in the control group. By the end of the study term, after the administration of the semaglutide, the semaglutide-treated group showed significantly lower blood glucose levels compared to the diabetic group with induced periodontitis.

Serum cytokine levels Assessment

Serum levels of inflammatory cytokines TNF-α, NF-ϰB, IL-1β, and IL-6 were measured and illustrated in table (2). When compared to the control group, the diabetic group with induced periodontitis had significantly higher levels of all four inflammatory parameters. The semaglutide-treated group displayed significant lower levels results of all four inflammatory markers (IL-1β, IL-6, NF-ϰB and TNF-α $= p < 0.001$) compared to the diabetic group with induced periodontitis. However, the results of the semaglutide-treated group were still greater than those of the control group.

TABLE (1) Comparison between the three studied groups according to body weight and Glucose level

	Control (n = 8)	**Diabetes + Periodontitis (n = 8)**	**Semaglutide-treated (n = 8)**	**F**	**p**
Body Weight (gm)					
Min. – Max.	220 – 280	190 – 230	162 – 186	54.883*	<0.001*
Mean ± SD.	251.8 ± 20.2	215.6[a] ± 12.1	175.5[ab] ± 9		
Sig. bet. grps.		$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
Glucose (mg/dl)					
Min. – Max.	78 – 101	310 – 380	95 – 200	210.30*	<0.001*
Mean ± SD.	90 ± 8.4	343.1[a] ± 26.3	145.3[ab] ± 35.5		
Sig. bet. grps.		$p_1<0.001^*$, $p_2=0.001^*$, $p_3<0.00^{1}*$			

***SD:* Standard deviation**

F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)

p: p value for comparing between the studied groups

p_1: p value for comparing between Control and Diabetes + Periodontitis

p_2: p value for comparing between Control and Semaglutide-treated

p_3: p value for comparing between Diabetes + Periodontitis and Semaglutide-treated

****: Statistically significant at $p \leq 0.05$***

a: significant with Control

b: significant with Diabetes + Periodontitis

TABLE (2) Comparison between the three studied groups according to cytokines

	Control (n = 8)	Diabetes + Periodontitis (n = 8)	Semaglutide-treated (n = 8)	F	p
IL-6 (pg/ml)					
Min. – Max.	90 – 150	285 – 330	187 – 210	302.658*	<0.001*
Mean ± SD.	111.5 ± 21.9	303.4[a] ± 14.1	200.5[ab] ± 7.2		
Sig. bet. grps.		p_1<0.001*, p_2<0.001*, p_3<0.001*			
IL-1β (pg/ml)					
Min. – Max.	60 – 85	210 – 310	95 – 135	181.356*	<0.001*
Mean ± SD.	74 ± 7.5	255.8[a] ± 31.2	119.1[ab] ± 12.4		
Sig. bet. grps.		p_1<0.001*, p_2=0.001*, p_3<0.001*			
TNF-α (pg/ml)					
Min. – Max.	50 – 72	175 – 230	120 – 163	191.772*	<0.001*
Mean ± SD.	60.3 ± 8	202.3[a] ± 19.7	148.3[ab] ± 13.9		
Sig. bet. grps.		p_1<0.001*, p_2<0.001*, p_3<0.001*			
NF-ϰB (ng/ml)					
Min. – Max.	0.77 – 1.9	6.9 – 8.2	4.1 – 5.2	404.416*	<0.001*
Mean ± SD.	1.2 ± 0.38	7.5[a] ± 0.53	4.7[ab] ± 0.42		
Sig. bet. grps.		p_1<0.001*, p_2<0.001*, p_3<0.001*			

SD: Standard deviation F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
p: p value for comparing between the studied groups p1: p value for comparing between Control and Diabetes + Periodontitis
p2: p value for comparing between Control and Semaglutide-treated
*p3: p value for comparing between Diabetes + Periodontitis and Semaglutide-treated *: Statistically significant at p ≤ 0.05*
a: significant with Control b: significant with Diabetes + Periodontitis

DISCUSSION

The bidirectional relationship between diabetes and periodontitis has been well-established in various studies.[22] A meta-analysis study demonstrated that diabetic subjects have an 86% higher risk of developing periodontitis, with changes in bone metabolism being the most common complication when diabetes and periodontitis coincide.[23] This study was carried out to evaluate the influence of semaglutide therapy, initially used for glycemic control, on the destructed periodontium.

In our current investigation, we made use of the STZ compound, which is extensively employed in experimental animal models for the induction of diabetes.[24] Its cellular mechanism involves permanent alterations to the genetic material, leading to fatal changes in cell metabolism.[25]

Semaglutide has been authorized as a medication for people with type 2 diabetes and is part of the class of incretin-based therapies, analogous to other agonists of the GLP-1 receptor. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones that are deactivated by dipeptidyl peptidase-4 (DPP-4). They work to boost the release of insulin by the pancreas in response to an oral intake of glucose through the

incretin effect.[26] Additionally, GLP-1 receptor agonists can reduce the apoptosis of pancreatic β-cells and stimulate their growth.[27] GLP-1 has additional functions, including enhancing muscle glucose absorption and decreasing hepatic glucose synthesis.[28] Drugs like semaglutide, which are GLP-1 analogs, have shown a decrease in hemoglobin A1C of around 1% as opposed to control groups in T2DM patients.[29] Accordingly, the current study's findings demonstrate that the semaglutide-treated group experienced a significant reduction in both glucose levels and body weight compared to the untreated diabetic group with periodontitis. Nauck et al. suggested that the reduction in body weight attributed to GLP-1 RA is due to its influence on the central nervous system and its shared mechanisms of action. These mechanisms include lowering calorie intake, slowing gastric emptying to avoid large post-meal spikes in blood sugar, suppressing glucagon secretion in hyperglycemia or euglycemia, and raising insulin in response to hyperglycemia.[30] Therefore, semaglutide is approved by the FDA for use as a pharmacologic treatment for obesity or as a prescription for overweight patients with comorbidities.[31]

Histological examination showed massive periodontal destruction in the diabetic group with induced periodontitis. It was manifested by obvious bone resorption and noticeable disorganization of periodontal ligament bundles. These changes were attributed to the extensive inflammatory process taking place due to periodontitis and aggravated by elevated glycemic levels.[32] Histological examination confirmed inflammatory cell infiltration with increased vasculature. Similarly, Choubaya et al. reported marked elevation in inflammatory infiltrate with alveolar bone loss in the periodontal tissue of diabetic rats with experimental periodontitis.[23]

The pronounced inflammation can be attributed to the increased release of catabolic cytokine release. Cytokine assessment in the present study demonstrated an intensive elevation in the levels of IL-1β, IL-6, TNF-α, and NF-ϰB. IL-1β stimulates the release of collagenase, an interstitial lytic enzyme, and a gelatin-degrading enzyme by fibroblasts during the course of periodontitis, resulting in matrix disintegration, connective tissue loss, and periodontal tissue destruction.[33] In addition, inflammatory mediators like TNF-α and IL-6 prevent osteoclast formation.[34] Furthermore, elevated blood glucose levels trigger the stimulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-ϰB), a crucial transcription factor needed for the induction of numerous inflammatory genes in periodontal fibroblasts, including TNF-α and IL-1β.[35]

Cytokine upregulation is credited to the accumulation of AGEs in the diabetic group. Elenkova et al. verified that the buildup of AGEs in the periodontium due to diabetes initiates the release of pro-inflammatory cytokines and reactive oxygen species, leading to heightened inflammation in the periodontal tissues.[36] In agreement, cytokine assessment in the present study demonstrated an intensive elevation in the concentrations of TNF-α, NF-ϰB, IL-1β, and IL-6. These outcomes align with those reported by Sakamoto et al., demonstrating that AGEs diminish the mRNA expression of osteoblast-related molecules and elevate the generation of inflammation-related molecules such as IL-1β. Subsequently, Sakamoto et al. also verified that AGEs elevate the concentrations of proinflammatory cytokines TNF-α and IL-6.[37] Moreover, RAGEs play a crucial role in damaging cellular processes. Binding of ligands to RAGE results in the elevation of oxidative stress and upregulation of NF-ϰB. In turn, NF-ϰB promotes the synthesis of proinflammatory cytokines that cause osteoclast differentiation, including TNF-α, IL-6, IL-17, and IL-1α and IL-1 β.[38] NF-ϰB activation also inhibits Fos-related antigen-1, a transcription factor crucial for the formation of bone matrix, leading to impaired formation of bone.[39]

On the other hand, the group treated with semaglutide showed a reduction in the inflammatory process, improved interradicular bone height, and

re-orientation of periodontal ligament bundles, along with decreased vasculature. The results emphasize the ability of semaglutide to effectively reduce inflammatory pathways in the body. This was established by analyzing cytokine levels in the group treated with semaglutide, which revealed a notable decrease in the levels of the four specific inflammatory cytokines that were studied, in comparison to the untreated diabetic group with periodontitis. In agreement, prior research suggested that semaglutide can adjust or decrease inflammatory processes. Shnaien et al. illustrated that semaglutide decreased the concentrations of IL-1β, IL-6, and TNF-α.[40] Similarly, Jiang et al. confirmed that semaglutide inhibited the activities of IL-6, NF-ϰB, and TNF-α.[41] Semaglutide is known to impact the immune system through various pathways. Immune cells, including eosinophils and neutrophils, contain GLP-1 receptors. When these receptors are activated, they can affect immune responses and inflammatory processes. McLean et al. verified that in mice, semaglutide decreases inflammatory cytokines like TNF-α and TGF-β1 in hepatocytes by activating GLP-1 receptors on endothelial and hematopoietic cells.[42] Besides, semaglutide reduces the activity of immune cells, which modifies immune system function. Semaglutide has been demonstrated by Rakipovski et al. to decreased leukocyte recruitment and rolling in mice.[43] Furthermore, semaglutide can reduce oxidative stress and therefore indirectly reduce inflammation. According to research by Li et al., semaglutide can lessen inflammation that is dependent on oxidative stress through an AMPK-dependent pathway. This results in a decrease in reactive oxygen species (ROS) as well as IL-1β, NF-ϰB, and TNF-α levels.[44]

Increased bone resorption-related disorders are largely attributed to the OPG/RANKL signaling pathway. An active osteoclast is responsible for bone resorption which is triggered by Receptor activator of nuclear factor kappa-B ligand (RANKL). By binding to the RANK receptor in osteoclast progenitor cells, this factor promotes osteoclast activation and differentiation. Additionally, Osteoprotegerin (OPG), which is secreted by osteoblasts, binds to RANKL and prevents osteoclast differentiation.[45] In rat models of T2DM induced by streptozotocin, Nuche-Berenguer et al. assessed bone metabolic markers. Results revealed a significant decrease in the OPG/RANKL ratio in T2DM leading to increased bone resorption.[46] In contrast, the GLP-1RAs class of antidiabetic medications, which includes semaglutide demonstrated beneficial effects in inhibiting bone resorption by modulating the OPG/RANKL/RANK system through upregulating OPG gene expression.[47]

CONCLUSION

Semaglutide exerts potent anti-inflammatory effects reflected in the reduction of the periodontal tissue breakdown and downregulation of bone resorption due to induced periodontitis in diabetic rats. Semaglutide is beneficial to be used not only to attain glycemic control in diabetic patients but also to improve periodontal status.

REFERENCES

1. Kononen E, Gursoy M, Gursoy UK. Periodontitis: A multifaceted disease of tooth-supporting tissues. *J Clin Med*. 2019;8(8).

2. Ramadan DE, Hariyani N, Indrawati R, Ridwan RD, Diyatri I. Cytokines and chemokines in periodontitis. *Eur J Dent*. 2020;14(3):483-495.

3. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, Rengo G. Periodontal disease: A risk factor for diabetes and cardiovascular disease. *Int J Mol Sci*. 2019;20(6).

4. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med*. 2020;10(4):174-188.

5. Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. *Diabetes Care*. 2010;33(8):1759-1765.

6. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos

P. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the international diabetes federation and the european federation of periodontology. *Diabetes Res Clin Pract*. 2018;137:231-241.

7. N Gurav A. Advanced glycation end products: A link between periodontitis and diabetes mellitus? *Curr Diabetes Rev*. 2013;9(5):355-361.
8. Akram Z, Alqahtani F, Alqahtani M, Al-Kheraif AA, Javed F. Levels of advanced glycation end products in gingival crevicular fluid of chronic periodontitis patients with and without type-2 diabetes mellitus. *J Periodontol*. 2020;91(3):396-402.
9. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: Evolving strategies for the treatment of patients with type 2 diabetes. *Metabolism*. 2011;60(1):1-23.
10. Yaribeygi H, Sathyapalan T, Sahebkar A. Molecular mechanisms by which glp-1 ra and dpp-4i induce insulin sensitivity. *Life Sci*. 2019;234:116776.
11. Bergmann NC, Davies MJ, Lingvay I, Knop FK. Semaglutide for the treatment of overweight and obesity: A review. *Diabetes Obes Metab*. 2023;25(1):18-35.
12. Tao LY, Lagosz-Cwik KB, Hogervorst JMA, Schoenmaker T, Grabiec AM, Forouzanfar T, van der Weijden FA, de Vries TJ. Diabetes medication metformin inhibits osteoclast formation and activity in in vitro models for periodontitis. *Front Cell Dev Biol*. 2021;9:777450.
13. Zhang Y, Yuan X, Wu Y, Pei M, Yang M, Wu X, Pang Y, Wang J. Liraglutide regulates bone destruction and exhibits anti-inflammatory effects in periodontitis in vitro and in vivo. *Journal of dentistry*. 2020;94:103310.
14. Moraes RM, Lima GM, Oliveira FE, Brito ACV, Pereira RC, Oliveira LD, Barros PP, Franco GC, Anbinder AL. Exenatide and sitagliptin decrease interleukin 1β, matrix metalloproteinase 9, and nitric oxide synthase 2 gene expression but does not reduce alveolar bone loss in rats with periodontitis. *Journal of Periodontology*. 2015;86(11):1287-1295.
15. In: *Guide for the care and use of laboratory animals*. 8th ed. Washington (DC)2011.
16. Shawky HA, Essawy MM. Myricitrin: A promising herbal therapy for periodontitis in immunosuppressed status. *Saudi Dent J*. 2023;35(5):515-524.
17. Bakac MS, Dogan A, Yilmaz MA, Altindag F, Donmez F, Battal A. Ameliorative effects of scutellaria pinnatifida subsp. Pichleri (stapf) rech.F. Extract in streptozotocin-induced diabetic rats: Chemical composition, biochemical and histopathological evaluation. *BMC Complement Med Ther.* 2023;23(1):410.
18. Cawthon CR, Blonde GD, Nisi AV, Bloomston HM, Krubitski B, le Roux CW, Spector AC. Chronic semaglutide treatment in rats leads to daily excessive concentration-dependent sucrose intake. *J Endocr Soc*. 2023;7(7):bvad074.
19. Araujo AA, Pereira A, Medeiros C, Brito GAC, Leitao RFC, Araujo LS, Guedes PMM, Hiyari S, Pirih FQ, Araujo Junior RF. Effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of periodontitis. *PLoS One*. 2017;12(8):e0183506.
20. Rehman HU, Ullah K, Rasool A, Manzoor R, Yuan Y, Tareen AM, Kaleem I, Riaz N, Hameed S, Bashir S. Comparative impact of streptozotocin on altering normal glucose homeostasis in diabetic rats compared to normoglycemic rats. *Sci Rep*. 2023;13(1):7921.
21. Leary SL, Underwood W, Anthony R, Cartner S, Corey D, Grandin T, Greenacre C, Gwaltney-Brant S, McCrackin M, Meyer R. Avma guidelines for the euthanasia of animals: 2013 edition. 2013.
22. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: A two-way relationship. *Br Dent J*. 2014;217(8):433-437.
23. Choubaya C, Chahine R, Zalloua P, Salameh Z. Periodontitis and diabetes interrelationships in rats: Biochemical and histopathological variables. *J Diabetes Metab Disord*. 2019;18(1):163-172.
24. Graham ML, Janecek JL, Kittredge JA, Hering BJ, Schuurman HJ. The streptozotocin-induced diabetic nude mouse model: Differences between animals from different sources. *Comp Med*. 2011;61(4):356-360.
25. Assadi S, Shafiee SM, Erfani M, Akmali M. Antioxidative and antidiabetic effects of capparis spinosa fruit extract on high-fat diet and low-dose streptozotocin-induced type 2 diabetic rats. *Biomed Pharmacother.* 2021;138:111391.
26. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: Systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012;344:d7771.
27. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: A review of their efficacy and tolerability. *Diabetes Care*. 2011;34(Suppl 2):S279.

28. Seufert J, Gallwitz B. The extra-pancreatic effects of glp-1 receptor agonists: A focus on the cardiovascular, gastrointestinal and central nervous systems. *Diabetes Obes Metab*. 2014;16(8):673-688.

29. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes A. 9. Pharmacologic approaches to glycemic treatment: Standards of care in diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157.

30. Nauck MA, Quast DR, Wefers J, Meier JJ. Glp-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021;46:101102.

31. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF, Group SS. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.

32. Choubaya C, Chahine N, Aoun G, Anil S, Zalloua P, Salameh Z. Expression of inflammatory mediators in periodontitis over established diabetes: An experimental study in rats. *Med Arch*. 2021;75(6):436-443.

33. Kc S, Wang XZ, Gallagher JEJJocp. Diagnostic sensitivity and specificity of host-derived salivary biomarkers in periodontal disease amongst adults: Systematic review. *J Clin Periodontol*. 2020;47(3):289-308.

34. Jiang Z-L, Cui Y-Q, Gao R, Li Y, Fu Z-C, Zhang B, Guan C-C. Study of tnf-α, il-1β and lps levels in the gingival crevicular fluid of a rat model of diabetes mellitus and periodontitis. *Dis Markers*. 2013;34(5):295-304.

35. Zheng J, Chen S, Albiero ML, Vieira GHA, Wang J, Feng JQ, Graves DT. Diabetes activates periodontal ligament fibroblasts via nf-kappab in vivo. *J Dent Res*. 2018;97(5):580-588.

36. Elenkova M, Tipton DA, Karydis A, Stein SH. Vitamin d attenuates human gingival fibroblast inflammatory cytokine production following advanced glycation end product interaction with receptors for age. *J Periodontal Res*. 2019;54(2):154-163.

37. Sakamoto E, Kido JI, Takagi R, Inagaki Y, Naruishi K, Nagata T, Yumoto H. Advanced glycation end-product 2 and porphyromonas gingivalis lipopolysaccharide increase sclerostin expression in mouse osteocyte-like cells. *Bone*. 2019;122:22-30.

38. C Tobon-Velasco J, Cuevas E, A Torres-Ramos M. Receptor for ages (rage) as mediator of nf-kb pathway activation in neuroinflammation and oxidative stress. *CNS Neurol Disord Drug Targets*. 2014;13(9):1615-1626.

39. Chang J, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, Guan K, Krebsbach PH, Wang CY. Inhibition of osteoblastic bone formation by nuclear factor-kappab. *Nat Med*. 2009;15(6):682-689.

40. Shnaien AA, Mohammad AR, Hassan ES. Neuroprotective effect of semaglutide in endotoxemia mouse model. *Iranian Journal of War Public Health*. 2023;15(2):1001-1007.

41. Jiang Z, Tan J, Yuan Y, Shen J, Chen Y. Semaglutide ameliorates lipopolysaccharide-induced acute lung injury through inhibiting hdac5-mediated activation of nf-ϰb signaling pathway. *Hum Exp Toxicol*. 2022;41:09603271221125931.

42. McLean BA, Wong CK, Kaur KD, Seeley RJ, Drucker DJ. Differential importance of endothelial and hematopoietic cell glp-1rs for cardiometabolic versus hepatic actions of semaglutide. *JCI Insight*. 2021;6(22).

43. Rakipovski G, Rolin B, Nohr J, Klewe I, Frederiksen KS, Augustin R, Hecksher-Sorensen J, Ingvorsen C, Polex-Wolf J, Knudsen LB. The glp-1 analogs liraglutide and semaglutide reduce atherosclerosis in apoe(-/-) and ldlr(-/-) mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci*. 2018;3(6):844-857.

44. Li Q, Tuo X, Li B, Deng Z, Qiu Y, Xie H. Semaglutide attenuates excessive exercise-induced myocardial injury through inhibiting oxidative stress and inflammation in rats. *Life Sciences*. 2020;250:117531.

45. Daniilopoulou I, Vlachou E, Lambrou GI, Ntikoudi A, Dokoutsidou E, Fasoi G, Govina O, Kavga A, Tsartsalis AN. The impact of glp1 agonists on bone metabolism: A systematic review. *Medicina*. 2022;58(2):224.

46. Nuche-Berenguer B, Moreno P, Esbrit P, Dapía S, Caeiro JR, Cancelas J, Haro-Mora JJ, Villanueva-Peñacarrillo MLJCti. Effect of glp-1 treatment on bone turnover in normal, type 2 diabetic, and insulin-resistant states. 2009;84:453-461.

47. Luo G, Liu H, Lu H. Glucagon-like peptide-1 (glp-1) receptor agonists: Potential to reduce fracture risk in diabetic patients? *British Journal of Clinical Pharmacology*. 2016;81(1):78-88.