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Effect of type 2 diabetes mellitus in adults undergoing fixed orthodontic treatment on proinflammatory chemokine profile and levels of advanced glycation in gingival crevicular fluid

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Abstract. – OBJECTIVE: The current study aims to reconnoiter the outcome of diabetes mellitus type 2 (DMT2) on levels of advanced glycation end products (AGEs) and pro-inflammatory chemokine in gingival crevicular fluid (GCF) of individuals undergoing fixed orthodontic treatment.

PATIENTS AND METHODS: Participants were divided into a diabetic and no-diabetic group according to inclusion and exclusion criteria. Power analysis was adopted from a previous study that reported GCF chemokines in obese individuals. All teeth were measured for clinical periodontal parameters (CPP). GCF and saliva were collected 3 months after placing stainless steel archwire. GCF was investigated for pro-inflammatory cytokines all expressed in pg/mL. Quantification of chemokines was performed using a Magnetic bead-based multiplex assay for the Luminex® platform. Non-normality of data was assessed by Mann-Whitney U-test. Normality was estimated using an Independent t-test. Descriptive data were computed in the form of standard deviations and means.

RESULTS: Unstimulated whole saliva flow rate (UWSFR) was significantly lower in diabetic patients compared to non-diabetics (p=.021). Amongst different clinical periodontal parameters (CPP) no difference in plaque scores (PS) and probing depth (PD) was found between diabetic and non-diabetic participants. Two GCF chemokines i.e., Resistin (p=.031) and AGEs (p=.017) were observed to be significantly higher in DMT2 participants compared to the non-diabetes group. CPP and GCF biomarkers in diabetic and non-diabetic individuals demonstrated a positive correlation between AGEs and GCF resistin levels concerning bleeding on probing (BoP) in diabetic patients.

CONCLUSIONS: Participants with DMT2 after alignment with an orthodontic device exhibited significantly high levels of resistin and AGEs. The proinflammatory response was noted in patients with hyperglycemia undergoing orthodontic treatment.

Key Words:

Fixed orthodontic, Diabetes mellitus, Proinflammatory chemokine, Advanced glycation end products, Clinical periodontal parameters.

Introduction

Diabetes mellitus type 2 (DMT2) is a major public health concern and the disease has increased four times in the last thirty years. The disease is prevalent both in developed and non-developed countries[1,2]. The usual presentation of DMT2 is poly urea, polydipsia, and unusual weight loss[3]. The manifestation includes the resistance of the body to normal insulin levels along with chronic hyperglycemia and low insulin production. Current evidence advocates that disease pathogenesis is linked with a state of chronic inflammation subclinically[4,5]. In a state of chronic hyperglycemia, different protein types undergo glycosylation leading to the formation of advanced glycation products (AGE) in soft tissues[6,7]. Cross-linking of collagen with AGEs takes place reducing the solubility with no reparative tendency for periodontal tissues[8]. Therefore, augmented AGEs levels with amplified cellular response reduce the periodontal structure rising susceptibility to periodontal breakdown[9].

Coordinated soft tissue remodeling within the surrounding bone and periodontal ligament during orthodontic tooth movement tail an asep-

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tic inflammatory response driven by an external force[10]. This results in osteoclastic activity in areas of compression whereas deposition of osteoblast in the zone of tension[6]. During orthodontic tooth movement, a series of secreted factors are expressed which are measurable in gingival crevicular fluid (GCF)[11,12]. These include tissue necrosis factor and interleukin, remodeling biomarkers of connective tissues matrix metalloproteinase-8 (MMP-8), and matrix metalloproteinase-9 (MMP-9) bone resorptive biomarkers kappa-B ligand (RANKL)[13]. The relationship between chronic systemic inflammation and raised A1c (HbA1c) is already established, and the possible implications for patients with DMT2 and periodontal disease are sure and unquestionable[11,14]. Individuals with DMT2 reveal diminished levels of proinflammatory cytokines level with periodontal conditions[15]. Therefore, having a higher incidence of developing periodontitis with poor periodontal healing outcomes[16].

Captivatingly, diabetes' effect on orthodontic tooth movement has been already studied on rat models demonstrating dubious results. Some evidence validates an increase in tooth movement while others show reduced orthodontic movement[6,9]. However, there are no studies to evaluate the rate of tooth movement in diabetes. At the molecular level, it is estimated diabetics have altered pro-inflammatory factors involved in osteoblastic or osteoclastic activity during orthodontic movements[15,16]. It has already been established that obese individuals experience subtle proinflammatory changes which significantly affect the rate of tooth movement[17,18]. The existing study is pillared on the same speculation among diabetes individuals. Therefore, the present study was constructed on the hypothesis that DMT2 alters the biochemical status of GCF in individuals seeking orthodontic treatment. The current study aims to reconnoiter the outcome of DMT2 on levels of AGEs and proinflammatory chemokine in GCF of individuals undergoing fixed orthodontic treatment.

Patients and Methods

Patients and Power Analysis

Patients were selected according to the following inclusion criteria. 1. Individuals who have never smoked 2. The age range of participants was 25-55 years 3. Individuals are declared as DMT2 according to the American Association of diabetics 2022. 4. Individuals undergoing fixed orthodontic treatment *via* MBT prescription 0.022-inch brackets along with archwire stainless steel for a minimum of 4 weeks. 5. Individuals who didn't use any Nonsteroidal anti-inflammatory drugs (NSAIDs) or any antimicrobial drugs in the last six months. DMT2 was confirmed through 8 hours of fasting blood sugar recorded at ≥126 mg/dL or 7.0 mmol/L. The confirmation was completed by testing HbA1C which gave results of ≥6.5% or 48 mmol/mol. The test was done using Glycohemoglobin Standardization Program (GSP) and Diabetes Control Trial assay. For assessment of body mass index (BMI) weight of the individual in kilograms was divided by height in meters squared[19]. Power analysis was adopted from a previous study that reported GCF chemokines in obese individuals. A sample of 25 participants was considered adequate in each group i.e., DMT2 and non-diabetic to obtain 80% power and 5% level of alpha.

Ethics, Settings, and Patient Consent

The present study followed the Declaration of Helsinki and agreed with STROBE (strengthening the reporting of observational studies in epidemiology) guidelines. The scientific committee of King Khalid University (KKU) approved the study. The orthodontic department of King Khalid University was engaged in the recruitment of the individuals. Written consent was granted by the participating individuals who were told about the purpose of the study and were allowed to withdraw at any point in time.

Sample Collection and Clinical Periodontal Parameters (CPP)

All teeth were measured for CPP. This included bleeding on probing (BoP), Plaque scores (PS), and Probing depth (PD) using a manual periodontal probe. A dichotomous scoring system was used for PS and BoP. Whereas PD was measured in millimeters from the base of the gingival sulcus and gingival margin. The dichotomous scale for PS and BoP is represented as 1: Presence of plaque and bleeding 2: Absence of plaque and bleeding.

The collection timings of GCF and saliva were in the morning between 8 am to 11 am during routine orthodontic consultancy. The samples were collected approximately 3 months after placing the stainless steel archwire. The unstimulated whole saliva flow rate was gathered in a milliliter/ 60 sec. Patients were requested to pool saliva in the oral cavity with no facial

muscle movement and to drool saliva in a falcon tube of 15 ml for 5 minutes. Similarly, GCF was congregated by isolating anterior lower teeth and removing supra gingival plaque. The teeth were dried and six perio strips were interleaved in the mesial sulcus of all teeth of the lower arch for 30 sec and pooled. Samples were discarded which contained blood and saliva traces. The capacity of GCF was evaluated using Periotron 8000. The recordings conspired against the flow rate and standard curve to assess the volume[19].

Lab-Based Quantification of Chemokines Pro-Inflammatory and AGEs

Perio strips along with collected GCF were transported to 20 IL of phosphate-based buffered saline and centrifugated for five minutes for 10000 rpm. Likewise, GCF was investigated for pro-inflammatory cytokines all expressed in pg/mL. For the reliability of the examiner, the Kappa score (k=0.87) was calculated showing good reliability. Quantification of chemokines was performed using a Magnetic bead-based multiplex assay for the Luminex® platform. The protocol was followed as recommended by the manufacturer. Color-coded beads were mixed with GCF samples and added to 96-well microplates coated already with analyte-specific antibodies. The antibody-antigen sandwich was made by binding GCF proteins with antibodies. Afterward, phycoerythrin-conjugated streptavidin was supplemented to fix the biotinylated detection antibodies. Beads were read on a dual-laser flow-based detection instrument (Luminex, Austin, TX, USA)[4,20].

Statistical Analysis

For statistical analysis, SPSS software was used (SPSS software, v21; IBM, Corp., Armonk, NY, USA). The homogeneity of the data was measured using the Shapiro-Wilk test. This was confirmed by plotting Q-Q graphs before the *p*-value valuation for the variable. Significance was set at .05. Non-normality of data was assessed by Mann-Whitney *U*-test. Normality was estimated using an Independent *t*-test. Descriptive data were computed in the form of standard deviations and means. Whereas data for chemokines were presented as means and ranges. For any correlation between levels of chemokines and CPP, Pearson correlation was used.

Results

The total number of participants was 50 i.e., 25 each in diabetic and non-diabetic groups. The mean age of participants in the diabetic group was 27.0±6.5 years. Whereas, participants in nondiabetic mean age was reported to be 26.3±6.3 years. In each group, females were more compared to men. There was no significant difference between age and gender between the groups ($p>0.05$). Biochemical analysis demonstrated Fasting plasma glucose (<.001); body mass index (.037) and hemoglobin A1c (<.001) to be statistically significant between the diabetic and non-diabetic groups. Oral hygiene was found to be comparable between the two experimental groups (Table I).

UWSFR and CPP of study participants were reported in Table II. UWSFR was significantly lower in diabetic patients compared to non-diabetics ($p=.021$). Amongst different CPP, no difference in PS and PD was found between diabetic and non-diabetic participants. However, a significant difference in BoP was seen between the two groups ($p=.034$).

GCF chemokines demonstrated a general upward trend among participants with DMT2. However, two GCF chemokines i.e., Resistin ($p=.031$) and AGEs ($p=.017$) were observed to be signifi-

Table I. General demographical characteristics of participants in the study group.

General characteristics	Diabetic group	Non-diabetic group	*p*-value
Number of participants	25	25	
Gender male/female	11\14	12\13	.81
Age (mean ± SD)	27.0 ± 6.5	26.3 ± 6.3	.62
Fasting plasma glucose (mean ± SD)	92.6 ± 6.1	130 ± 5.9	< **.001**
Body mass index (mean ± SD)	26.9 ± 1.8	21.6 ± 1.1	**.037**
Hemoglobin A1c (mean ± SD)	7.6 ± 0.8	5.1 ± 0.7	< **.001**
Brushing frequency %			.87
Once-daily	18	10	
Twice daily	82	90	

Bold and italics numbers indicate a statistically significant difference between groups at $p < 05$.

Table II. Unstimulated whole saliva flow rate (UWSFR) and CCP of study participants.

Characteristics	Diabetic group	Non-diabetic group	*p*-value
UWSFR, mL/min (mean ± SD)	0.55 ± 0.21	0.79 ± 0.33	**.021**
PD, mm (mean ± SD)	3.1 ± 1.2	2.0 ± 1.1	.088
BoP % (mean ± SD)	17.6 ± 2.8	9.5 ± 1.6	**.034**
PS, % (mean ± SD)	15.8 ± 4.2	14.2 ± 3.5	.699

Bleeding on Probing BoP; Probing depth PD; Plaque scores (PS). *p*-value was determined using an independent *t*-test. Bold and italics numbers indicate a statistically significant difference between groups at $p < .05$.

cantly higher in DMT2 participants compared to the non-diabetes group (Table III). Pearson correlation analysis between CPP and GCF biomarkers in diabetic and non-diabetic individuals demonstrated a positive correlation between AGEs and GCF resistin levels concerning BoP in diabetic patients (Table IV).

Discussion

The present study was created on the assessment to reconnoiter levels of GCF pro-inflammatory chemokines and AGEs in participants with diabetes and without diabetes and to appraise the effect of diabetic status on the chemokine profile in individuals undergoing fixed orthodontic treatment. The levels of adipocyte-specific hormone resistin and AGEs (formed when proteins or lipids are glycated as a result of exposure to sugars) demonstrated a significant difference in patients with diabetes Mellitus. Further, both AGEs and resistin showed a positive correlation with BoP in diabetic participants.

The design of the present cross-sectional study was performed cautiously to include harmonized cohorts for both participants diabetic and non-diabetics. However, the biochemical variable was unable to be matched due to the nature of the cohort with diabetic status (exposure). It was significant that the BMI of diabetic patients was substantially higher than non-diabetic participants. The BMI of diabetic patients was 26.9±1.8 which is already considered to be overweight but not in the category of obese. A recent study by Saloom et al[4] showed obese individuals to have increased metabolic leptin and remodeling tissue chemokines, this proposed an upsurge in proinflammatory chemokines in obese patients in the final stages of fixed orthodontic treatment[4]. Future studies should be directed to assess the harmonized effect of obesity and diabetes mellitus type 2 on the chemokines in the GCF in participants undergoing fixed orthodontic treatment.

The participants with diabetes mellitus showed decreased flow of saliva in comparison to non-diabetics. This significant reduction in the production of saliva in a given cohort may be attributed to systemic health issues in patients with DMT2. As already established rigorous oral care is linked with a low amount of microbial plaque[21]. This is practiced habitually in fixed orthodontic treatment in which patients

Table III. GCF of study participants with Proinflammatory Biomarkers and advanced glycation end product (AGEs).

Variables	Diabetic	Non-diabetic	*p*-value
GCF flow rate, l L/min	0.99 ± 0.44	0.95 ± 0.11	.498
Tumor necrosis factor-alpha pg/mL	100.85 (88.41-112.44)	88.22 (68.54-91.65)	.759
Interleukin-6 pg/mL	62.97 (49.25-71.66)	46.25 (39.25-65.47)	.587
Ghrelin, ng/mL	86.29 (60.55-83.98)	77.69 (63.25-87.29)	.984
Resistin, ng/mL	34.25 (11.25-18.69)	15.25 (1287-17.98)	**.031**
Advanced glycation end product (AGEs) pg/mL	388 (340.25-487.45)	228.58 (198.99-298.35)	**.017**
Receptor activator of nuclear factor kappa-B ligand (RANK-L) pg/mL (range)	1271.87 (1187.33-1363.25)	1174 (1088.36-1147.39)	.258

p-value was determined using Mann-Whitney U-test. Bold and italics numbers indicate a statistically significant difference between groups at $p < .05$.

Table IV. Pearson Correlation analysis between CPP and GCF biomarkers in diabetic and non-diabetic individuals.

Variables	Tumor necrosis factor-alpha	Interleukin-6	Ghrelin	Resistin	AGE	RANK-L
PS						
Non-diabetic group	-.2147	-0.5847	0.7415	0.7854	-0.8412	-0.847
p-value	.8414	.1547	.0609	.3225	.6547	.4176
Diabetic group	0.8477	0.3698	0.5144	0.897	0.6541	0.2528
p-value	.8955	.0987	.0965	.7654	.4658	.2547
BoP						
Non-diabetic group	0.8714	-0.7514	0.5621	0.7412	-0.4742	0.7825
p-value	.8954	.4569	.0785	.8147	.0854	.5874
Diabetic group	-0.7847	0.5487	0.4784	0.1487	0.0187	0.6587
p-value	.1478	.0746	.6565	***.0121***	***.0147***	.3547
PD						
Non-diabetic group	0.6587	0.7821	0.4854	0.4569	0.8547	0.4785
p-value	.2547	.8543	.9268	.5471	.4174	.5871
Diabetic group	.8743	0.8746	0.7621	0.2587	0.9836	0.9874
p-value	0.9532	.1366	.2987	.9214	.74147	.8547

Bold and italics numbers indicate a statistically significant difference between groups at $p < .05$.

with fixed ortho devices are specified to perform strict hygiene measures to decrease plaque accumulation around soft gingival tissue[22,23]. Both diabetic and non-diabetic cohorts established low plaque scores. This is reflected by the frequency of toothbrushing twice daily in both groups by more than 80% of the participants[24,25]. However, the proportion of bleeding was found to be significantly higher among participants of DMT2 compared to non-diabetics. High bleeding is allied to heightened glycemic levels. Evidence suggests chronic diabetes/hyperglycemia is linked with substantial inflammatory response around periodontal tissues linked with preeminent biomarker IL-1β[26,27].

The level of Resistin was higher in patients with DMT2. This verdict can be attributed to a sharp chronic systemic inflammatory state and chronic expression of pro-inflammatory resistin locally in the periodontium. Similarly, high levels of resistin correspond to the osteoclastic activity which is related to bone remodeling. Furthermore, resistin may also be released by neutrophils due to alteration in plaque composition in patients with DMT2[28,29]. High levels of AGEs were observed in diabetic patients indicating an embellished inflammatory response that results in alveolar bone and soft tissue destruction in DMT2[30]. Surprisingly, the role of resistin and AGEs in orthodontics tooth movement, and bone remodeling are skeptical, dubious, and unclear in patients with DMT2. Therefore more control trials are recommended to measure the levels of AGEs and resistin when aligning the teeth with fixed orthodontics at different intervals of the treatment.

Individuals with DMT2 should be cautious in maintaining oral hygiene during orthodontic treatment. Also, hyperglycemia tempers pathogens of periodontal tissues and may further deteriorate periodontal health along with elevated chemokine levels in patients undergoing orthodontic treatment.

Conclusions

Participants with DMT2 after alignment with an orthodontic device exhibited significantly high levels of resistin and AGEs. The pro-inflammatory response was noted in patients with hyperglycemia undergoing orthodontic treatment.

Conflict of Interest

The Author declares that there was no conflict of interest.

Informed Consent

Written consent was obtained by the participating individuals who were told about the purpose of the study and were allowed to withdraw at any point.

Funding

None.

Ethics Approval

The Scientific Committee of King Khalid University (KKU) approved the study. The present study followed the Declaration of Helsinki and agreed with STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.

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