European Review for Medical and Pharmacological Sciences 2023; 27: 755-762

Efficacy of subgingival minocycline hydrochloride delivery as an adjunct to non-surgical mechanical debridement for the treatment of peri-implantitis in patients with type-2 diabetes mellitus

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Abstract. – OBJECTIVE: The aim was to assess the efficacy of subgingival minocycline hydrochloride (MH) delivery with non-surgical mechanical debridement (NSMD) for treating peri-implantitis in patients with type-2 diabetes mellitus (DM).

PATIENTS AND METHODS: Type-2 diabetic and non-diabetic patients with peri-implantitis were included. In the test-group, patients underwent NSMD with a single session of MH delivery. In the control-group, patients underwent NSMD alone. Hemoglobin A1c (HbA1c), modified plaque-index (mPI), modified gingival index (mGI), probing-depth (PD) and crestal bone loss (CBL) were measured at baseline and at 6-month follow-up. Level of significance was set at p<0.01.

RESULTS: Thirty type-2 diabetic and 30 healthy individuals with peri-implantitis were included. There was a significant reduction in mPI (p<0.01), PD (p<0.01) and mGI (p<0.01) at 6 months among patients with and without type-2 DM in the test and control groups. There was no significant difference in peri-implant parameters in all patients at the 6-month follow-up. There was no significant difference in HbA1c and CBL among patients with and without type-2 DM in the test and control groups when baseline values were compared with those at 6 months of follow-up.

CONCLUSIONS: A single application of subgingival MH delivery is as effective as NSMD alone for the treatment of peri-implantitis in type-2 diabetic patients.

Key Words:
Alveolar bone loss, Minocycline hydrochloride, Type-2 diabetes mellitus, Probing depth, Peri-implantitis.

Abbreviations

AGE: advanced glycation endproducts; CBL: crestal bone loss; HbA1c: Hemoglobin A1c; MH: minocycline hydrochloride; mPI: modified plaque-index; mGI: modified gingival index; T2D: Type-2 diabetes; NSMD: non-surgical mechanical debridement; HSPT: non-surgical periodontal therapy; PD: probing depth; PIS: peri-implant sulcular fluid; RCT: randomized controlled trial.

Introduction

Non-surgical mechanical debridement (NSMD) of implant surfaces and peri-implant sulci is the conventional therapy adopted for the management of peri-implant diseases[1]. Numerous therapies including antibiotic and probiotic therapy, photobiomodulation, and photodynamic therapy have been proposed to facilitate healing of peri-implant tissues when used as adjuncts to NSMD compared with MD alone[2-5]; however, the most reliable or efficient adjunct therapy in this regard remains unknown. Systemic antibiotics are often prescribed for the management of periodontal and peri-implant diseases as they exert an antimicrobial effect and facilitate healing[6,7]. When using systemic antibiotics for the management of infectious and inflammatory diseases, the risk of superinfections cannot be overlooked[1,2]. Scientific evidence[10,11] has shown that local antibiotic delivery provides an antimicrobial platform by providing a synergistic effect of "contact-killing". Minocycline hydrochloride (MH) is a semisynthetic derivative of tetracycline; and is commonly used for the

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treatment of various oral and systemic bacterial infections including respiratory infections, and urinary tract infections, and periodontitis[12-15]. In a recent experimental study on male beagle dogs, Qian et al[12] induced peri-implant osseous defects around bone-level implants placed in the region of missing second and third mandibular premolars. Implants in the test group were treated with subgingival MH applications on implant abutments, whereas those in the control group received no treatment. The histologic results[12] showed a larger quantity of neutrophils and osteocytes around peri-implant defects in the test compared with the control group. The authors concluded that local MH delivery prevents the progression of peri-implantitis[12].

Poorly-controlled type-2 diabetes (T2D) is a well-known systemic risk factor of periodontal and peri-implant diseases[16-18]. Chronic hyperglycemia, a classical manifestation in poorly-controlled DM is associated with an increased formation and accumulation of advanced glycation endproducts (AGE) in the periodontal tissues. The AGE augment inflammation by increasing the expression of destructive inflammatory cytokines in the gingival crevicular fluid and peri-implant sulcular fluid (PISF) thereby worsening the overall soft tissue and osseous inflammatory response[17,19,20]. Moreover, a positive correlation exists between expression peri-implant probing depth (PD) and expression of AGEs in the PISF[17,21]. It is therefore anticipated that outcomes of oral interventions and wound healing are compromised in patients with poorly-controlled DM. In a randomized controlled trial (RCT), Lin et al[20] assessed the effect of non-surgical periodontal therapy (NSPT) with and without subgingival MH administration in patients with poorly-controlled T2D. The results showed that NSPT with or without subgingival MH administration significantly reduces periodontal inflammatory parameters (plaque index, gingival index and PD) in patients with poorly-controlled T2D. With reference to the results from the Lin et al's study[20], it is hypothesized that NSMD with or without subgingival MH administration reduces peri-implant modified plaque index (mPI), modified gingival index (mGI) and PD and minimizes the risk of further crestal bone loss (CBL) in patients with type-2 DM.

Therefore, this RCT assessed the efficacy of subgingival MH delivery as an adjunct to NSMD for the treatment of peri-implantitis in patients with T2D.

Patients and Methods

Inclusion and Exclusion Criteria

Patients with T2D diagnosed with peri-implantitis were included. Diagnosis of peri-implantitis was based on the following parameters: (1) bleeding on gentle probing or/and suppuration, (2) PD ≥4 mm, (3) recession of peri-implant mucosal margin (implant thread exposure) and (4) radiographic CBL ≥2 mm[22]. Self-reported current nicotinic product users (including electronic nicotine delivery systems and smokeless tobacco), former smokers, habitual alcohol consumers and patients with systemic diseases other than DM (such as cardiovascular disorders, renal and hepatic diseases, and patients with viral infections such as HIV) were excluded. Patients with existing or a history of periodontitis and nursing and/or pregnant females were excluded. Furthermore, patients that reported to have undergone NSPT and/or consumed steroids, antibiotics, non-steroidal anti-inflammatory drugs, probiotics and/or bisphosphonates within 90 days were excluded.

Study Location, Design and Participants

The present RCT was performed at a tertiary healthcare center situated in Riyadh, Saudi Arabia between February and September 2021. All patients were residents of Riyadh, ArRiyadh province, Saudi Arabia.

Randomization, Grouping, Allocation Concealment and Blinding

Type-2 diabetic and non-diabetic participants with peri-implantitis were randomly divided into test and control groups. In the test group, patients underwent NSMD and full mouth ultrasonic scaling around natural teeth with adjunct subgingival MH application. In the control group, patients underwent NSMD and full-mouth ultrasonic scaling (FMUS) around natural teeth only. Randomization was done using an online service by www.sealedenvelope.com. The principal investigator (TA) concealed the allocation of the participants.

Assessment of Hemoglobin A1c Levels

In all patients, HbA1c levels were checked preoperatively and after 6 months by a calibrated investigator (NAH; Kappa 0.9) using an HbA1c analyzer kit (Quo-Test, EKF Diagnostics, Magdeburg, Germany). The HbA1c levels were measured during early morning hours with the participants being in a self-reported fasting state.

Hyperglycemic and normoglycemic individuals were classified as individuals with a HbA1c of ≥6.5% and less than or equal to 5.5%, respectively[23,24].

Questionnaire

Demographic data was collected using a questionnaire. Information regarding drug allergies (especially tetracycline allergy), duration of T2D, treatment used for the management and T2D and family history of DM was also collected. Medical records of the participants were also evaluated to verify the diagnosis of T2D.

Non-Surgical Mechanical Debridement and Periodontal Therapy

In patients with and without T2D, peri-implant, NSMD was performed at baseline and at the 6-month follow-up using plastic curettes (Hu-Friedy®, Chicago, IL, USA); and full mouth NSPT was performed using sterile stainless steel hand instruments (Hu-Friedy®, Chicago, IL, USA) and an ultrasonic scaler (Dental Equipment Woodpecker Uds-J Ultrasonic Scaler EMS Compatible Original, Guangzhou, China). The NSMD and NSPT were performed by a trained investigator (YA).

Subgingival Minocycline Hydrochloride Delivery

In the study cohort, individuals in the test group underwent subgingival MH administration in the deepest peri-implant buccal sulci immediately after NSMD. The peri-implant region was isolated with sterile cotton rolls; and a specifically designed disposable plastic syringe was gently inserted in the deepest peri-implant sulcus and continued to be moved down until resistance was felt. The MH microspheres (ARESTIN®, Bausch Health Companies Inc., Laval, Canada) were then gently released into the sulcus and the tip was slowly withdrawn. Each unit-dose cartridge delivered MH equivalent to 1 mg of minocycline free base. Patients in the test group were instructed to refrain from eating and drinking for at least 30 minutes after the procedure.

Peri-implant Clinical and Radiographic Parameters

Baseline and 6-month follow-up clinical and radiographic investigations were performed by one trained and calibrated examiner who was blinded to the study participants (factor V; Kappa score 0.88). Peri-implant mPI[25], mGI[25,26], and PD[25] were measured at four sites per implant. Probing measurements were made using a light force (approximately 0.3 N). Mesial and distal CBL were measured on digital bitewing radiographs (Intra oral X-Ray-Systems - NOMAD/ Pro-2, Gendex, Hatfield, PA, USA) using the long-cone paralleling technique[27,28]. Implant location (maxilla and/or mandible), dimensions (length and diameter), depth of placement (crestal or subcrestal), loading protocol (immediate, early or delayed) and duration in function in years was also recorded.

Sample-Size Estimation

Sample size estimation (SSE) was done using data from a pilot study. The SSE was based on the assumption that a 3-mm reduction in mean peri-implant PD would occur in the test group with 0.6 mm standard deviation; and a 2-mm reduction in the control group with 0.5 mm standard deviation. It was estimated that with inclusion of at least 14 patients in test and control groups, respectively, the study would have 80% of statistical power, and an alpha of 5%.

Statistical Analysis

Statistical analyses were done using the Mann-Whitney U test and one way analysis of variance. For multiple comparisons, Bonferroni Post-hoc adjustment test was performed. Logistic regression analysis was done to assess the correlation between peri-implant parameters and HbA1c levels. Level of significance was set at $p<0.05$.

Results

Questionnaire

Thirty patients with self-reported T2D (19 males and 11 females) and 30 self-reported systemically healthy individuals (20 males and 10 females) with peri-implantitis were included. In each group, the participants were randomly divided into test and control groups with 15 patients per subgroup. There was no significant difference in mean ages of all patients. Duration of DM in the test and control groups was 6.7 ± 1.6 and 6.08 ± 1.3 years, respectively. Family history of DM was more often reported by patients with than without T2D (Table I). There were no known drug allergies reported by patients with and without T2D.

Table I. Demographics of the study cohort.

Parameter	Patients with type-2 diabetes mellitus (n = 30)		Patients with type-2 diabetes mellitus (n = 30)	
	Test group	Control group	Test group	Control group
Participants (n)	15	15	15	15
Gender	10 males 5 females	9 males 6 females	9 males 6 females	11 males 4 females
Mean age	52.7 ± 6.3 years	55.5 ± 3.7 years	52.6 ± 5.7 years	54.3 ± 4.1 years
Duration of type-2 DM	6.7 ± 1.6 years	6.08 ± 1.3 years	NA	NA
Family history of DM	6 (40%)	7 (46.7%)	2 (13.3%)	None
Implants (n) (Maxilla: mandible)	15 (1: 14)	15 (4: 11)	15 (3: 12)	15 (4: 11)
Duration of implants in function	7.4 ± 0.5 years	6.8 ± 0.2 years	6.5 ± 0.3 years	7.2 ± 0.4 years

DM: Diabetes mellitus; HbA1c: Hemoglobin A1c.

A total of 30 (5 in the maxilla and 25 in the mandible) and 30 implants (7 in the maxilla and 23 in the mandible) with peri-implantitis were present in the patient population. All implants were platform switched and were located in the regions of missing premolars and molars. All implants were placed at bone level in healed arches and were loaded with cement-retained restorations. The implants were in function for 7.4 ± 0.5 and 6.8 ± 0.2 years in the test and control groups in patients with T2D; and for 6.5 ± 0.3 and 7.2 ± 0.4 years in the test and control groups in patients without T2D (Table I). All implants had moderately rough surfaces and had lengths and diameters ranging between 4.1 and 5 mm and 11 and 13 mm, correspondingly. None of the participants presented with adverse reactions, such as intra or extraoral swelling, face rash, and/or headache up to 6 months of follow-up.

Peri-Implant Parameters

At baseline, there was no significant difference in peri-implant mPI, mGI, PD and mesial and distal CBL in patients with and without T2D. There was a statistically significant reduction in mPI ($p<0.01$), mGI ($p<0.01$), PD ($p<0.01$) at 6 months among patients with and without T2D in the test and control groups. There was no significant difference in peri-implant mPI, mGI, and PD among patients with and without T2D in the test and control groups at 6 months of follow-up. There was no significant difference in HbA1c and CBL among patients with and without T2D in the test and control groups when baseline values were compared with those at 6 months of follow-up. There was no significant difference in the mean HbA1c levels of individuals in the test and control groups among patients with and without T2D (Table II).

Correlation Between Peri-Implant Parameters and Hba1c Levels

There was no statistically significant correlation between peri-implant mPI, mGI, PD, mesial and distal CBL with HbA1c, gender, duration of implants in function, and implant jaw location in the test and control groups among patients with and without T2D.

Discussion

In the present study, that authors hypothesized that NSMD with or without subgingival MH administration reduces peri-implant inflammatory parameters (mPI, mGI and PD) and minimizes the risk of further CBL in patients with poorly-controlled T2D. Our results are in partial agreement with this hypothesis as the 6-month follow-up results showed a statistically significant reduction in peri-implant soft tissue inflammatory parameters in all patients that underwent NSMD either with or without adjunct subgingival MH delivery. In the present study, the inclusion of patients with T2D was chiefly based on the diagnosis of the metabolic disease and not stringently on a poor control of T2D. An impaired or elevated glycemic status in patients with DM is a risk factor of periodontal and peri-implant diseases[29-32]. Interactions between AGEs and their receptors are primarily held responsible for inducing oxidative stress (OS) in gingival tissues and increasing the production if destructive cytokines such as

Table II. Peri-implant parameters and hemoglobin A1c levels at baseline in the study groups.

	Baseline				6-month follow-up			
	Patients with type-2 diabetes mellitus (n = 30)		Patients without type-2 diabetes mellitus (n = 30)		Patients with type-2 diabetes mellitus (n = 30)		Patients without type-2 diabetesmellitus (n = 30)	
Peri-implant parameters	Test group	Control group	Test group	Control group	Test group	Control group	Test group	Control group
mPI	2.7 ± 0.3*	2.5 ± 0.2†	2.5 ± 0.3‡	2.4 ± 0.1§	1.2 ± 0.2	1.02 ± 0.04	0.8 ± 0.05	1.05 ± 0.07
mGI	3.2 ± 0.2*	2.8 ± 0.06†	2.8 ± 0.1‡	3 ± 0.2§	0.6 ± 0.1	0.6 ± 0.08	0.5 ± 0.07	0.7 ± 0.05
PD	5.7 ± 0.3 mm*	5.3 ± 0.2 mm†	5.3 ± 0.2 mm‡	5.5 ± 0.3 mm§	1.7 ± 0.2 mm	2 ± 0.08 mm	1.8 ± 0.1 mm	1.5 ± 0.08 mm
CBL (mesial)	4.6 ± 0.07 mm	4.5 ± 0.4 mm	4.3 ± 0.1 mm	4.5 ± 0.2 mm	4.3 ± 0.02 mm	4.5 ± 0.07 mm	4.2 ± 0.05 mm	4.2 ± 0.07 mm
CBL (Distal)	4.6 ± 0.2 mm	4.5 ± 0.1 mm	4.2 ± 0.2 mm	4.5 ± 0.1 mm	4.4 ± 0.1 mm	4.3 ± 0.1 mm	4.4 ± 0.1 mm	4.2 ± 0.04 mm
HbA1c	6.1 ± 0.2	6.3 ± 0.08	4.2 ± 0.08	4.3 ± 0.1	5.7 ± 0.2	6.05 ± 0.2	4.2 ± 0.2	4.2 ± 0.3

CBL: Crestal bone loss; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; mm: millimeters; mPI: modified plaque-index; mGI: modified gingival index; PD: probing depth. *Compared with the test group in patients with type-2 DM at the 6-month follow-up ($p < 0.01$); †Compared with the control group in patients with type-2 DM at the 6-month follow-up ($p < 0.01$), ‡Compared with the test group in patients without type-2 DM at the 6-month follow-up ($p < 0.01$); §Compared with the control group in patients without type-2 DM at 6-month follow-up ($p < 0.01$).

interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) that enhance osteoclastic activity[29-32]. Therefore, peri-implant soft tissue inflammation and CBL were expected to be worse in patients with T2D in comparison with patients without T2D. However, the results showed that at baseline peri-implant parameters were similar in patients with and without T2D. This is possibly associated with the HbA1c levels of patients with T2D included in the present study. We observed no statistically significant difference in HbA1c levels among patients with T2D and non-diabetic individuals and dietary control and routine use of antihyperglycemic medications could have played a role in keeping HbA1c levels below 8%, a classic marker of poor glycemic control[24]. It is therefore speculated that although OS in gingival tissues in patients with T2D was high enough to induce signs of peri-implant disease but not elevated enough to demonstrate a significant difference in peri-implant mPI, mGI, PD and CBL compared with non-diabetic individuals. The mere explanation for peri-implantitis in patients without T2D is poor oral hygiene maintenance as reflected by their mPI, mGI, PD scores. The authors agree with the study by Al-Amri et al[33] in which, poor oral hygiene maintenance was named as the most common reason for peri-implant diseases including peri-implantitis in patients with and without T2D.

The authors support the results of a 6-month follow-up RCT in which, Lin et al[20] assessed the effect of NSPT with or without adjunct subgingival MH in T2D patients with periodontitis. The authors reported no significant difference in clinical periodontal parameters among diabetic patients that underwent NSPT with or without adjunct subgingival MH administration; and suggested that this could have occurred due to a small sample-size[20]. Although the results of the present investigation were power-adjusted, no significant difference in peri-implant parameters were evident at 6-month follow-up. It is noteworthy that in the present RCT, subgingival MH administration was done once throughout the study period. There are conflicting results regarding the possible role of NSPT towards reduction in HbA1c levels[20,34]. In the present study, reduction in HbA1c levels among diabetic patients was noted; however, when compared with baseline, HbA1c levels recorded at the 6-month follow-up were statistically insignificant. It is speculated that multiple subgingival MH administrations (one at the day of NSMD and another after 3 months) are needed to expect a significant reduction in HbA1c, clinical peri-implant inflammatory parameters and new bone formation in type-2 diabetic and non-diabetic patients with peri-implantitis. This warrants additional studies.

In the present RCT, efficacy of subgingival MH administration as an adjunct to NSMD was assessed on clinical and radiographic grounds primarily due to limitations in funding sources. It is known that presence of pathogenic bacteria such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia* in the subgingival oral biofilm contribute towards the etiology of peri-implant diseases[35,36]. Moreover, destructive inflammatory cytokines such as IL-1β and TNF-α are also associated with CBL and progression of peri-implantitis in susceptible patient populations[37,38]. In an *in vitro* experiment, Qian et al[10] showed that MH when loaded on titanium by graphene-oxide shows antibacterial activity against gram-positive and gram-negative bacteria. From a microbiological and immunoinflammatory perspective, it is hypothesized that in contrast to NSMD alone, subgingival MH application as an adjuvant antimicrobial therapy is more effective in reducing subgingival colonization of pathogenic bacteria; and is also helpful in minimizing the volume of PISF and expression of destructive inflammatory cytokines in this biologic fluid. There is a lack of consensus regarding as to whether surgical MD is superior to NSMD for the treatment of peri-implantitis[39]. It remains to be determined whether surgical MD with adjunct local MH admiration provides superior outcomes in terms of treatment of peri-implantitis compared with surgical MD alone. Further well-designed and power adjusted RCTs are needed to test these hypotheses.

Conclusions

A single application of subgingival MH delivery is as effective as NSMD alone for the treatment of peri-implantitis in patients with T2D.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors are grateful to the Researchers supporting project at King Saud University for funding through Researchers supporting project (RSP2023R44), Riyadh, Saudi Arabia.

Ethics Approval

The present study was performed following guidelines recognized by the Declaration of Helsinki as revised in 2013 for experimentation involving human patients. Ethical approval was obtained from the Ethics Research Committee of Centre for Specialist Dental Practice and Clinical Research (UDCRC/025-16).

Informed Consent

All volunteering individuals were requested to read and sign a consent form. All participants were informed that they could withdraw their participation at any phase of the study without consequences.

Authors' Contribution

T. Abduljabbar designed the study and supervised the research project. K.M. Ali performed the clinical investigations. N. Al-Hamoudi administered the questionnaire. F. Vohra performed the statistical analysis. K.M. Ali read and revised the manuscript prior to submission. T. Abduljabbar, K.M. Ali and F. Vohra wrote the discussion. K.M. Ali performed the mechanical debridement. All authors read and approved the manuscript prior to submission.

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