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Original Article

A microbiological assessment of peri-implant sites and implant-abutment interfaces in diabetic and healthy individuals

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Abstract: Although diabetes has been postulated as a risk factor for peri-implantitis, research on this subject has been very limited. The purpose of this study was to evaluate the microbiological profiles in peri-implant sites and the implant-abutment interface in diabetic and healthy implant recipients. The same root-form implant was used in all the participants. 360 samples were collected at 4 different time points (2, 14, 30, and 90 days after surgery) from 2 different locations (the peri-implant site and the implant-abutment interface) in triplicate. In the collected samples, 4 pathogens associated with both periodontitis and peri-implantitis were counted using quantitative polymerase chain reactions. At the peri-implant sites, no statistical differences in the number of the investigated species were observed between the healthy and diabetic patients at any time point. The number of bacteria in the implant-abutment interface increased with the implantation time. However, no significant difference was observed between the healthy and diabetic patients at the implant-abutment interface. The profiles of the major pathogens in the peri-implant site and the implant-abutment interface were not affected by diabetes. These findings are in accordance with previous studies.

Keywords: Peri-implantitis, diabetes, implant-abutment interface, bacterial colonization

Introduction

With the substantial increase in the use of dental implants, inflammatory conditions caused by pathogenic bacteria around the implant (peri-implantitis) have become a serious problem that needs to be addressed [1]. Peri-implantitis exhibits many similarities to inflammation of the periodontal tissues (periodontitis) [2, 3]. However, distinctions in the histopathology of periodontitis and peri-implantitis have been reported as well [4]. This is to be expected because of the micro-roughness of the implants, which aims to increase cellular adhesion, which also increases the bacterial adhesion to the implant, resulting in a colonization of bacteria that is normally not associated with periodontitis [5, 6]. Despite some differences, the etiology, prognosis and treatment of periodontitis and peri-implantitis are very similar, and a history of periodontitis has been shown to increase the risk of peri-implantitis [2, 7].

Systemic diseases, diabetes in particular, have been identified as a significant risk factor for periodontitis [8-10]. Poorly controlled diabetes especially increases the propensity for gingivitis and periodontitis [11, 12]. Moreover, based on the similarities between periodontitis and peri-implantitis, diabetes has been postulated as a risk factor for peri-implantitis or dental implant failures.

Several long-term studies have been performed to determine the success rate of dental implants in diabetic patients. Multiple systematic literature reviews on this subject have con-

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Male or Female	- Having a systemic disease other than DM T2.
- Age ≥ 18	- Having bad oral hygiene and/or prevailing periodontitis.
- Partially edentulous	- Having undergone antibiotic treatment at least 3 months prior to the implant placement.
- Confirmed diagnosis of diabetes mellitus Type 2 (DM T2) by an endocrinology clinic (For the patient group)	- Having undergone immune-suppressant treatment at least 3 months prior to the implant placement.
- Being systematically healthy (For the control group)	- Use of prosthetic and/or orthodontic devices.
- Signed agreement on the informed consent form	- Use of medication known to affect bone healing (bisphosphonates, etc.).
	- Habit of smoking or tobacco chewing.
	- Having conditions that affect saliva flow such as xerostomia, radiotherapy, etc.
	- Being pregnant or breastfeeding.
	- Having an infectious disease known to be transmitted by saliva.
	- Inability to understand the content of the informed consent form.

cluded that diabetes does not statistically affect the implant success rates compared to implants in healthy patients [13-15]. Based on this evidence, diabetes is not now thought to be a significant risk factor affecting the implant success rate. However, implant success rates are determined mostly by clinical parameters, such as peri-implant bone loss or implant loss; therefore, peri-implantitis needs to be investigated separately from implant success rates. Peri-implantitis is a serious condition that needs to be treated, but it has been shown to be the cause of only a small percentage of implant losses [16] as it can manifest with or without peri-implant bone loss [17]. Research on the correlation between diabetes and peri-implantitis has been limited so far. The possible role of delayed wound healing and the compromised immune system of diabetic patients in peri-implantitis is yet to be evaluated [18]. This evaluation is imperative for determining the routine care methods for diabetes patients receiving dental implants and for planning treatment in case of the development of peri-implantitis.

In addition to the peri-implant inflammation, the bacterial colonization of internal voids of the implants, such as the implant-abutment interface (IAI), has been reported to contribute to peri-implant bone loss [19] and peri-implantitis [20]. However, no studies were found regarding the colonization of the IAI in diabetic patients.

In this study, our aim was to carry out a microbiological comparison of both the peri-implant sites and the internal surfaces of the implants between well controlled diabetes mellitus type 2 (DM T2) and healthy implant recipients.

Material and methods

Patient selection

This study was carried out at the Oral and Maxillofacial Surgery Department of a Dentistry Faculty and was approved by the "Local Ethical Committee on Non-Drug Clinical Studies" on 17 February 2016 (File Number: 0045). Patients who applied to the clinic between August 2017 and February 2018 with partial edentulism were evaluated for this study. 7 well-controlled DM T2 patients and 8 systemically healthy individuals met the inclusion and exclusion criteria (**Table 1**). The periodontal health of each participant was evaluated using radiographs, full mouth pocket depth, clinical attachment level, plaque and gingival index values to ensure there was no prevailing periodontal disease. The general oral hygiene conditions of each participant were determined by intra- and extra-oral examination. Patients with prevailing periodontal disease or poor oral hygiene were not included in

Table 2. Demographics of the participants

		Healthy	DM T2	TOTAL
GENDER	Female	5	2	7
	Male	3	5	8
	Total	8	7	15
AGE	Total	46 ± 9	61 ± 13	53 ± 13

this study. DM T2 patients with glycated hemoglobin (HbA1c) levels between 6.1 and 7 were included in this study.

Implant placement

The same root-form implant system (SwissPlus, Zimmer Biomet, IN, USA) was used for all patients. Implants were placed using a 1-stage process. Upon obtaining informed consent, the patients were administered local anesthetics (Articaine with 1/100,000 epinephrine). After performing a total thickness mucoperiosteal flap extension, conventional drilling was carried out for the implant insertion. The implants were inserted using a manual ratchet with an average torque of 40 N.cm torque. Cover screws were placed into the implants using finger force. The muco-periosteum was adapted and sutured with resorbable poly glycolic acid sutures (Neocryl Rapid, Setpa LLC, İzmir, Turkey). No bone augmentation or additional surgery was performed for the implant insertion. No prosthetic abutment was attached, and no load was applied on the implants throughout the study.

Sample collection

Saliva samples were collected at 2, 14, 30, and 90 days after the surgery (DAS) using sterile absorbent endo paper points. The paper points were placed in the peri-implant sites and were rotated around for 30 seconds to cover all the surfaces of the implant. To collect samples from the implant-abutment interface (IAI), the cover screws were removed, and paper points were rotated inside the implants for 30 seconds. Care was taken to prevent contamination of the paper points with saliva by isolating the implant site with cotton rolls and gauze pieces. 3 to 5 paper points were used for each peri-implant and IAI site. A total of 360 specimens were collected. After the sample collection, the paper points were placed in sterile microcentrifuge tubes and stored at -20°C until the time of analysis. At the end of the collection period, the samples were shipped to an independent laboratory for analysis (Admera Health, LLC, NJ, USA).

Bacterial count

Four pathogens associated with both periodontitis and peri-implantitis, *Aggregatibacter actinomycetemcomitans* (A.a.), *Porphyromonas gingivalis* (P.g.), *Tannerella forsythia* (T.f.), and *Treponema denticola* (T.d.), were investigated in this study. The bacterial counts were performed using quantitative real-time polymerase chain reaction (q-PCR). The genes used for the q-PCR analysis were 23S ribosomal RNA gene for A.a. and P.g., chaperonin groL for T.f. and 16S ribosomal RNA gene for the T.d. Primer and probe designs. The DNA isolation and the q-PCR protocols were carried out by an independent, specialized laboratory (Admera Health, LLC, NJ, USA).

Statistical analysis

The comparisons of the bacteriological counts between the groups at each timepoint for each pathogen were done using independent samples *t*-tests. The changes in bacteriological counts with time were analyzed using repeated measures one-way analysis of variance (RM-ANOVA). The level of significance was set to $p \leq 0.05$ for all analyses. The data quality control and statistical analyses were done using IMB SPSS Statistics Version 25 (IBM SPSS, Chicago, IL).

Results

The demographics of the participants are listed in **Table 2**. No failed implants were reported for the duration of the study. The bacteriological counts were done at the peri-implant sites and the implant-abutment interface (IAI).

The bacterial counts from the peri-implant sites in the healthy and DM T2 groups are shown in **Table 3**. At the peri-implant sites; no significant differences were observed between the healthy and the DM T2 groups at any time point for any bacteria ($P>0.05$) (**Table 3**). The repeated measures ANOVA tests showed no statistically significant differences in the bacterial count change with time for any of the investigated species in the healthy and the DM T2 groups ($P>0.05$) (**Figure 1**).

Table 3. Bacterial counts (mean ± SD CFU) from the peri-implant sites in healthy and DM T2 groups and the significance levels (p) from the t-test

DAS	Groups	*A.a.*	*P.g.*	*T.f.*	*T.d.*
2	Healthy	14292 ± 7884	18849 ± 4437	21417 ± 4899	29255 ± 12906
	DM T2	12546 ± 8935	18988 ± 7641	20934 ± 8538	22461 ± 6983
	p	*.785*	*.970*	*.195*	*.254*
14	Healthy	15821 ± 9371	20206 ± 5214	18317 ± 7254	27331 ± 15937
	DM T2	17516 ± 8363	16742 ± 4130	27585 ± 11433	25977 ± 7887
	p	*.895*	*.205*	*.109*	*.847*
30	Healthy	16772 ± 8974	17255 ± 5317	20386 ± 7812	30017 ± 11090
	DM T2	19257 ± 8614	18531 ± 5271	23883 ± 10215	32153 ± 12584
	p	*.593*	*.672*	*.508*	*.753*
90	Healthy	20078 ± 10204	19631 ± 6867	22451 ± 9095	37416 ± 18526
	DM T2	18645 ± 10012	20062 ± 3050	24481 ± 12112	41822 ± 11991
	p	*.919*	*.889*	*.844*	*.615*

DAS: Days after surgery.

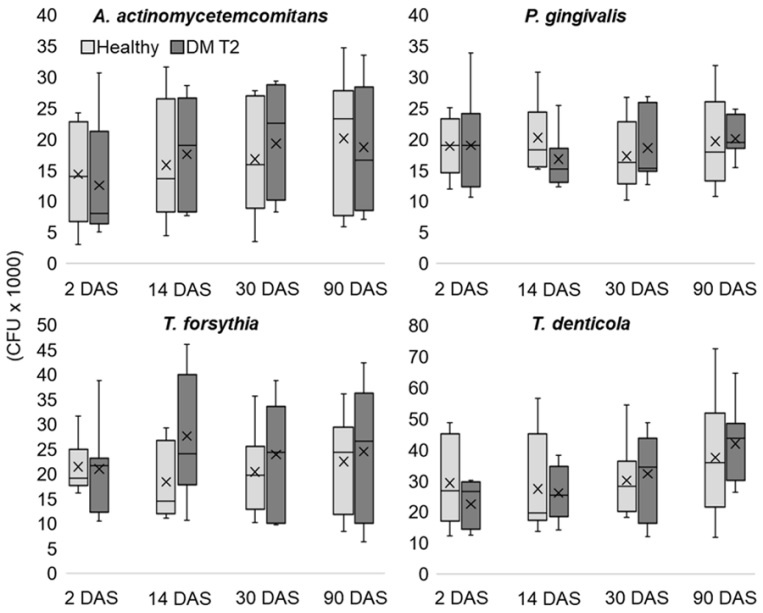

Figure 1. Timewise bacterial profiles in the peri-implant sites of the healthy and DM T2 groups. (x: mean, -: median).

The significant differences in the bacterial counts in the IAI between time points were determined by ANOVA after repeated measures (**Table 4**). A.a. and T.f. appeared to colonize the IAI earlier in the DM T2 patients. For A.a., a significant difference from 2 DAS was observed at 90 DAS in the healthy group, but in the DM T2 group, the significant difference from 2 DAS was observed at 30 DAS, meaning the IAI was colonized faster in the implant patients with DM T2. Similarly, for T.f., the level of significance between the time points was much higher in the DM T2 patients compared to the healthy group (**Table 4**). On the other hand, for T.d., a significant difference was observed earlier (14 DAS) in the healthy group when compared to the DM T2 group (90 DAS). When each time point was compared separately, no significant differences were observed between the healthy and the DM T2 groups at any time point for any of the analyzed bacteria at the implant-abutment interface (P>0.05) (**Table 5**; **Figure 2**). No pattern was observed between the healthy and the DM T2 groups in terms of colonization of the IAI by the analyzed bacteria.

Discussion

Periodontitis, and likewise peri-implantitis, are diseases with a bacteriological origin. Peri-implantitis differs from periodontitis in the sense that it is a site-specific inflammation rather than a specific host response.

Several risk factors have been identified for periodontitis, such as systemic disease, old age, genetic susceptibility, etc. [21-23]. Diabetes has been considered as a risk factor for peri-implantitis or implant failure in general, as well [18]. However, several retrospective and

Table 4. Comparison of the significance levels (*p* values) of the bacterial count in the IAI obtained from the Repeated ANOVA analysis

	Healthy					DM T2				
		2 DAS	14 DAS	30 DAS	90 DAS		2 DAS	14 DAS	30 DAS	90 DAS
A.a.	2 DAS		.999	.377	**.008**	2 DAS		.258	**.042**	**.027**
	14 DAS			.650	**.013**	14 DAS			.389	.294
	30 DAS				.076	30 DAS				.357
P.g.		2 DAS	14 DAS	30 DAS	90 DAS		2 DAS	14 DAS	30 DAS	90 DAS
	2 DAS		.103	**.026**	**.002**	2 DAS		.062	**.076**	**.020**
	14 DAS			.999	.738	14 DAS			.999	.333
	30 DAS				.614	30 DAS				.704
T.f.		2 DAS	14 DAS	30 DAS	90 DAS		2 DAS	14 DAS	30 DAS	90 DAS
	2 DAS		**.012**	**.021**	**.003**	2 DAS		**.001**	**.006**	**.001**
	14 DAS			.999	.443	14 DAS			.275	**.018**
	30 DAS				.841	30 DAS				.508
T.d.		2 DAS	14 DAS	30 DAS	90 DAS		2 DAS	14 DAS	30 DAS	90 DAS
	2 DAS		**.022**	**.010**	**.001**	2 DAS		.093	.078	**.012**
	14 DAS			.215	.076	14 DAS			.397	.312
	30 DAS				.999	30 DAS				.999

Significant differences are highlighted with bold (DAS: Days after surgery).

Table 5. Bacterial counts (mean ± SD CFU) from the implant-abutment interface in the healthy and DM T2 groups and the significance levels (p) from the *t*-test

DAS	Groups	*A.a.*	*P.g.*	*T.f.*	*T.d.*
2	Healthy	22077 ± 8374	5639 ± 3174	21818 ± 16813	13739 ± 8263
	DM T2	19178 ± 5514	4873 ± 2479	21718 ± 19821	21150 ± 12451
	p	*.470*	*.634*	*.999*	*.242*
14	Healthy	26315 ± 10894	14982 ± 9419	66900 ± 30558	39988 ± 12436
	DM T2	32348 ± 14413	13207 ± 7054	62423 ± 17982	38696 ± 11447
	p	*.419*	*.705*	*.749*	*.849*
30	Healthy	40728 ± 21745	17180 ± 9585	77623 ± 33235	54069 ± 18289
	DM T2	49725 ± 16364	19318 ± 10455	83084 ± 21550	49849 ± 17430
	p	*.411*	*.709*	*.728*	*.678*
90	Healthy	73009 ± 23382	20684 ± 8036	87860 ± 23262	65358 ± 17341
	DM T2	57562 ± 18991	26921 ± 11073	99731 ± 26483	50417 ± 16037
	p	*.212*	*.274*	*.411*	*.131*

DAS: Days after surgery.

prospective studies investigating the implant success rates in diabetic patients have revealed that the outcomes of dental implants treatments in diabetes patients are satisfactory and practically the same with non-diabetic individuals [24-27]. It is now accepted that diabetes, especially when well-controlled, is not a contraindication for dental implant treatment.

The microbiological aspects of periodontitis and peri-implantitis in healthy individuals have also been studied extensively. The microbiota of peri-implantitis has been shown to be more complex than that of periodontitis [2, 28]. This is mainly due to the different adhesion abilities of bacteria to the titanium implant surfaces [29, 30]. However, in addition to the pathogens thought be specific to peri-implantitis, prominent microorganisms involved in periodontitis have been shown to be involved peri-implantitis as well [2, 31].

The microbiological aspects of peri-implantitis in diabetes patients are a less investigated

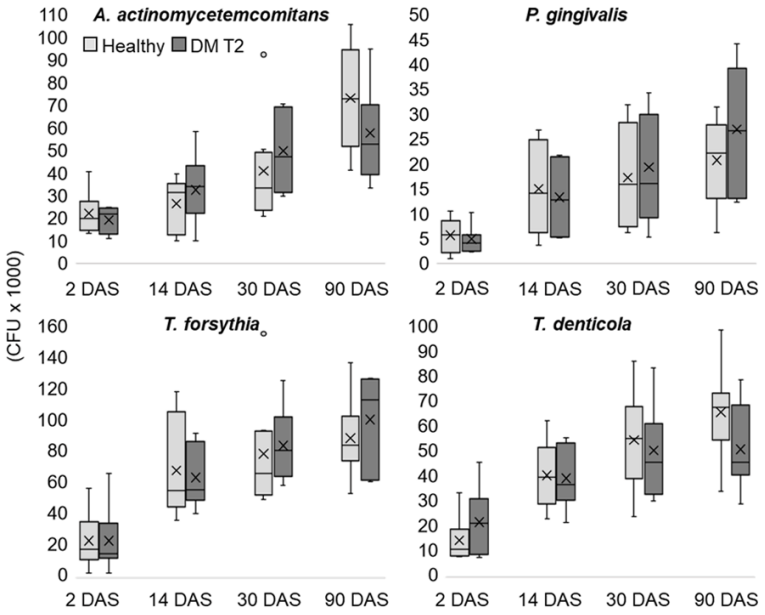

Figure 2. Timewise bacterial profiles in the implant-abutment interface of the healthy and DM T2 groups. (x: mean, -: median).

subject. Aguilar-Salvatierra *et al.* reported that the prevalence of peri-implantitis was higher among diabetes patients with higher HbA1c levels [32]. However, no comparison with healthy individuals were done in this study and only DM T2 patients with different HbA1c levels were investigated. There are also studies reporting no association with diabetes and peri-implantitis [33, 34]. However, these studies were carried out based on the clinical parameters of peri-implantitis, such as pocket depth, radiological findings, etc., and no microbiological analyses were done.

In a study by Bignozzi *et al.,* both the clinical and microbiological profiles of diabetic and healthy implant patients were investigated. They reported no significant differences in the microbiological profiles of the peri-implant sites between healthy and diabetic implant patients [35].

In our study, the colonization of the peri-implant sites and the IAI was investigated in well-controlled DM T2 and healthy implant patients by the species prominently associated with periodontitis but also observed in peri-implantitis. In the peri-implant sites, our findings agree with the study by Bignozzi *et al.* [35]. We observed no significant differences in the bacterial counts of the investigated species between healthy and DM T2 implant patients.

To the best of our knowledge, there are no other studies investigating the colonization of the IAI in diabetic patients. As expected, an increase in the bacterial count in the IAI was observed over time in both the healthy and DM T2 groups. The implants are sterile when packaged and placed under aseptic conditions, but the IAI has been shown to be colonized eventually [36, 37]. A.a. and T.f. were observed to colonize the IAI earlier in DM T2 patients, but colonization by T.d. occurred sooner in the healthy individuals. P.g. appeared to colonize the IAI at around the same time in both the healthy and DM T2 implant patients. Based on these results, no clear pattern in the time of IAI colonization between the healthy and the DM T2 groups was deduced.

Another point to be noted is the comparison of the bacteria count in the peri-implant sites and the IAI. At 90 DAS, the average number of bacteria in the IAI was 2 to 3 times higher compared to the peri-implant sites in both the healthy and diabetic patients (**Tables 3**, **5**). The micro-leakage of saliva is the main reason for the colonization of the IAI. Therefore, the general design of the implant, which determines the close fitting between the implant fixture and the prosthetic abutment, has been shown to affect the colonization of the IAI [38]. In this study, the bacterial counts in the IAI were done while the cover screws, which are used before the attachment of the prosthetic abutment, were attached. The cover screws are not as closely fitted as the prosthetic abutments since they are placed with finger pressure only. This may result in a substantial micro-leakage into the IAI before placement of the prosthetic abutment. Since the internal colonization of the implants is a significant contributor to the peri-implant inflammation, a general cleaning of the IAI is advised in both healthy and DM T2 patients before the attachment of the prosthetic abutment.

Within the limitations of the study (the small number of participants, relatively short observation time, lack of clinical parameters), our findings support the notion that DM T2, when well-controlled, is not a risk factor for peri-implantitis. The higher susceptibility of DM T2 patients to peri-implantitis observed in some studies may be due to the consequences of secondary factors, such as hyperglycemia and an upregulated immune response rather than differences in the peri-implant microflora.

Conclusion

The microbiological profiles of the investigated species were not statistically different either in the peri-implant tissues or in the IAI for the healthy and DM T2 implant patients. Further studies involving parameters such as radiological assessments, microbiological assessment of a wider range of pathogens, the level of osseointegration, and metabolic parameters could help better explain the correlation between diabetes and peri-implantitis.

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Disclosure of conflict of interest

None.

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