Clinical Performance of Titanium-Zirconia Tissue-level Implants in Patients with Well-controlled and Poorly-controlled Type 2 Diabetes: A cohort study with chair-side assessment of oxidative stress

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ABSTRACT

Purpose. Diabetes is associated to systemic oxidative stress. This might jeopardize implant therapies. The aim of this cohort study was to investigate the survival and success rates of titanium-zirconia implants in patients with a history of type 2 diabetes (T2DM) according to glycemic control and oxidative stress levels.

Methods: Patients with T2DM of ≥2-year duration were allocated to either the well-controlled (HbA1c≤< 53 mmol/mol) or poorly-controlled (HbA1c>53 mmol/mol) groups in a prospective cohort fashion. Patients received titanium implants with a zirconia trans-gingival neck. Then, patients were followed at intervals for at least 1.5 years. Clinical and radiographic parameters describing implant success were collected. Rapid chair-side test for the peripheral blood and salivary oxidative stress were performed with spectrophotometer analysis and measured in U CARR units.

Results: Thirty-seven implants in twenty-eight patients have been included in the analysis. The 1-year implant survival and success rates were 100%. No signs or symptoms of mucositis/peri-implantitis were recorded up to the last follow-up visit. The blood test for oxidative stress scored an average value of 367±71.8 U CARR, with no differences on the basis of glycemic control. The average salivary test score for oxidative stress was 2203±364 U CARR, which is within the limits of a healthy range. This test was found to be higher in diabetic patients showing poor glycemic control.

Conclusion: Tissue level implants with a zirconia neck are a reliable solution in diabetic patients with varying levels of glycemic con-

trol and oxidative stress, as long as the general oral health is preserved.

Keywords: diabetes, saliva, zirconia, implant, oxidative stress

INTRODUCTION

Diabetes is one of the most common chronic metabolic diseases and represents the third leading cause of mortality worldwide [1]. Diabetes plays an important role in the development of cardiovascular diseases by means of increased systemic oxidative stress. In fact, elevated blood glycemic levels lead to more free oxygen radicals and peroxidation of fatty acids affecting normal cell metabolism [2].
Diabetes increases the odds of developing periodontitis and tooth loss [3-5]. Periodontal disease and tooth loss are more frequent among diabetic patients, even after adjusting for different confounding factors. Therefore, diabetic patients often need implant therapy. For years, diabetes has been considered a contraindication to implant therapy due to the supposed higher risk for failure, peri-implantitis, and early loss of osteointegration [6].
According to the recent systematic review by SoutoMaior and colleagues, there is no effect of diabetes on the survival rate of implants, but a negative effect of the disease could be observed on marginal bone loss [7]. In fact, chronic inflammation and oxidative stress associated to hyperglycemia affect angiogenesis and the critical anabolic events needed for bone formation [8].
For decades, the golden standard for implant therapy has been the two-stage Branemark procedure, as this approach should be safer and able to prevent early infection and loss of osteointegration, especially in a patient at risk [8]. However, in submerged implants or two-part implants, the implant-abutment interface is located at the bone level, unreachable to cleaning devices and posing a risk for resorption of the immediate peri-interface bone as a result of local granular inflammatory demarcation [9-11]. Different approaches have been proposed to overcome this inevitable inflammatory phenomenon, mainly: the platform switching concept and the transmucosal tissue-level implant [12-13]. Tissue level implant dislocates the inflammatory burden in a coronal direction, far away from the bone, thus preventing marginal bone resorption and favoring the establishment of an early soft tissue seal [14-15].
Zirconia showed great success at maintaining marginal soft tissue stability around fixed dental prosthesis [16]. Later, zirconia has been associated to connective tissue stability and increased fibroblasts collagen production in histologic studies [17].
Different data arising from sialo-chemistry studies in diabetic patients showed that saliva reflects human plasma biomolecular composition [18-19].
The primary aim of this cohort study was to investigate the survival and success rates of titanium implants with a tissue-level zirconia neck in patients with a history of type 2 diabetes (T2DM) and to do a stratification of the outcome according to glycemic control and oxidative stress levels.

MATERIALS AND METHODS

Study design and participants

This cohort study was based on patients treated on a routine basis at one specialistic center (Istituto Stomatologico Toscano, Lido di Camaiore, Italy) between 2018 and 2021. Patients who were willing to participate were asked to sign a written informed consent, in which scopes and methods of the current protocol were detailed.
Patients aged 18-85 years with a diagnosis of T2DM ≥ 2 years in duration, and requiring implant therapy were included in the study. Patients were stratified according to their present glycemic control in two groups: "well controlled" if showing HbA1c< 53 mmol/mol and "poorly controlled" if showing HbA1c>=53 mmol/mol. Exclusion criteria were pregnancy or lactation, smokers, bi-

sphosphonates therapy, a history of chronic steroid use, periodontal disease, osteoporosis, immunodeficiencies, ridge atrophies requiring bone augmentation procedures.

The present study was approved by the CHLN and CAML Lisbon Ethical Committee with identity number 350/18. All study procedures complied with the principles stated in the Declaration of Helsinki "Ethical Principles for Medical Research Involving 'Human Subjects", adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and as amended most recently by the 64th World Medical Assembly, Fontaleza, Brazil, October 2013. Research activities and reporting were conducted in compliance with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines (http://www. strobe-statement.org/).Surgical protocol and implant-related characteristics

Tissue-level implants were placed under local anesthesia with a flapless approach. TBR® implants (Toulouse, Francia) "Z1-Connect"® with a zirconia 1.5 mm collar and varying lengths (10.5 to 13 mm) were used. The surgeon placed the implants leaving the zirconia collar outside the bone margin.

Each patient was prescribed amoxicillin (2 g orally one hour before surgery, followed by 500 mg 2 times a day for 5 days). Pain was controlled by topic application of gaseous ozone (DTA, Sweden & Martina) once a week for the first month and painkillers were prescribed only if necessary. Oral hygiene instructions were given with visual aids, and patients were also recommended to rinse with an antioxidant mouthwash product containing lactoferrin (Polifarma Benessere) twice daily for 2 weeks. Until 2 years of follow-up, all patients had been enrolled in a strict dental prophylaxis program in which they had received complete debridement using an ultrasonic scaler and reinforcement of oral hygiene instructions every three months.

Loading protocol and prosthesis-related characteristics

The conventional loading was performed 3-4 months after implant placement. Master models and precision impressions were obtained using digital transfer impression copings and the intraoral dental scanner (Carestream Dental CS3600). All crowns were fabricated by the same dental laboratory following the standard procedures. Custom abutments were molded and then, crowns were torqued (35 Ncm) according to the manufacturer's recommendation. The rehabilitation occlusion was checked to not interfere with patient's existing physiologic occlusion. In addition, centric contacts were kept light in the maximum intercuspidation and complete disocclusion was ensured during eccentric movements to prevent inconvenient lateral levers.

Clinical and radiographic parameters

Peri-apical radiographs obtained via the long-cone paralleling technique with a loop film holder (Rinn, Dentsply Australia Pty Ltd, Pacific Hwy, St Leonards NSW 2065, Australia) were used to measure the marginal bone levels at 3 months interval up until the last follow-up visit. Radiographs were standardized by means of individual resin bites. The distance between the implant–abutment interface and the first bone-to-implant contact (fBIC) on mesial and distal surfaces was recorded. The scale was calibrated on the width of the dental implant (fixed measure) achieving a unique pixel/mm ratio. Radiographic bone levels were calculated at the moment of prosthetic transfer connection (impression taking) and 12 months after loading. The mean marginal bone level (MBL) for each implant was computed merging mesial and distal values. The marginal bone change was defined as the difference between the last follow-up and the baseline MBL value, with negative values denoting a loss in bone height. All measurements were performed by the same investigator. Measurements were performed with the OsirisX software (Pixmeo SARL, 266 Rue de Bernex, CH-1233 Bernex, Switzerland). Six-point peri-implant probing depths (PPD) measured with a standardized 15 mm periodontal probe and bleeding on probing (BOP) were documented at all follow-up visits.

Survival and Success Criteria

Implant failure was coded as the eventual implant mobility or persistent infection, and whenever the implant presented signs and/or symptoms that led to implant removal.
Survival and success rates (SRs and CSRs, respectively) for implants, were calculated according to the criteria defined by Buser et al. in 1997 [20]. Successful implants were those showing a mean radiological peri-implant bone resorption within 1.5 mm during the first year of loading, and less than 0.2 mm/year during the following years.

Hemoglobin A1c levels

HbA1c levels were retrieved from the updated current records of the patients's physicians before surgeries and at the last follow-up visit.

Oxidative stress measures

Blood samples were taken from the fingertip between 07:00 am and 08:00 am and were immediately kept on ice and centrifuged at 3,000×g for 5 min. The plasma samples (approximately 100 µl per patient) were used to determine plasma levels of reactive oxygen species. Samples were processed according to instructions furnished by the producer (H&D s.r.l.). The d-ROMs (derived reactive oxygen metabolites) test determined the concentration of hydro-peroxides in the blood. Its unit of measurement is the U CARR (0.08 mg/dL of a solution of hydrogen peroxide). Values higher than 300 U CARR pose for a pathological systemic condition of the redox system.
Saliva samples were taken after a night of fasting between 07:00 am and 08:00 am keeping patients from rinsing with anything but water. Saliva was collected by letting the patient chew on a sterile gauze for 10 seconds. The salivary antioxidant test (SAT) evaluates the salivary total antioxidant capacity and its unit of measure is vitamin C µmol/L o µM. Values higher than 2500 U CARR denote the presence of local oxidative stress. Saliva was immediately analyzed since it degenerates soon altering the absorbance properties of the sample.
Oxidative stress measures were collected at baseline at at the last-follow-up visit.

Statistical Analysis

Descriptive and inferential statistic analysis was performed using R version 3.6.3 (2020-02-29) -- "Holding the Windsock" (www.r-project.org/), a free software environment for statistical computing and graphics. Normality of distribution of the variables was confirmed with Q–Q plots. The implant was the statistical unit used for the analysis and but a further mixed effect model (function lmer within package lme4) was used to control for crossed random effects posed by patients contributing with more than one implant. This formula expects that there is going to be multiple responses per patient, and these responses will depend on each subject's baseline level. This effectively resolved the non-independence that stemmed from having multiple responses by the same subject. The Welch Two Sample T test was used to investigate relations among different variables with normal distribution.

RESULTS

Data demographics

In total, 37 implants were placed in 28 patients with a mean age of 50.3 years (range 21–80 years), and the average follow-up period was 1.6 ± 0.5 years (mean ± SD). The longest follow-up period was 2.6 years, and 100% of the implants had a follow-up of at least 1 year. The cumulative implant survival rate was 100%, with no implant loss. The demographic data of the patients are described in Table 1. Implants were placed mostly in the premolar area (64.8%).
Eighteen out of 28 patients were "well controlled" (HbA1c<53 42 mmol/mol) and 10 patients were "poorly controlled" (HbA1c<53 42 mmol/mol). The mean duration of T2DM was 16.1±11.1 years. The mean glycated hemoglobin level was 49.2±4.35 mmol/mol. All

patients with T2DM had been prescribed anti-hyperglycemic medications by healthcare physicians and were also advised to maintain their glycemic levels via dietary control. Medication type was comparable between groups

value of 367±71.8 U CARR which was to be expected in a diabetic cohort, with no difference in the subgroups stratified on the basis of glycemic control (p-value = 0.312; 95 percent confidence interval: lower -49.69717 upper

Table 1. Demographics of the study participants and clinical outcomes for both groups.

Parameters	Total	Well controlled	Poorly controlled	P-value
Number of individuals	28	18	10	
Gender (M/F)	17/11	12	16	>0.05
Age (mean±SD)	50.3 years (range 21–80)	49.5±4.50	52.0±3.50	>0.05
Baseline HbA1c mmol/mol	50.3±4.30	44.2±4.30	54.1±3.35	<0.05
1-year HbA1c mmol/mol	49.2±4.35	45.6±3.21	53.1±3.30	<0.05
Insulin	10	1	9	<0.05
Metformin	18	17	1	<0.05
1-year Survival	100%	100%	100%	>0.05
1-year Success	100%	100%	100%	>0.05
1-year Bone loss (mm)	0.2±0.2	0.2±0.4	0.3±0.1	>0.05
1-year dROM (UCARR)	367±71.8	355±61.9	404±88.7	>0.05
1-year SAT (UCARR)	2203±364	2133±274	2433±249	<0.05

(P > 0.05), except for insulin which was used with significantly higher frequency by subjects in the poorly controlled group (P = 0.01) (Table 1).

Clinical outcomes

At the moment of analysis, all 37 implants were healthy, thus, the implants had a cumulative survival rate of 100%. No failure, defined as signs and symptoms that led to implant removal, or patients' complaint could be recorded. No radiological marginal bone loss extending the first thread neither 1.5 mm apical to the platform could be observed. Therefore, the cumulative success rate was 100%. Peri-implant soft tissues appeared healthy and thick at the last follow-up (Fig 1).

Oxidative stress status

The systemic dROMs test scored an average

134.94478) (Fig 2).

The average SAT was 2203±364 U CARR which is within the limits of a healthy oral status, however, the SAT test was found to be higher in diabetic patients showing a poorly controlled glycemic status (p-value = 0.003; 95 percent confidence interval: lower 146.8610 upper 601.7866) (Fig 3).

DISCUSSION

This study analyzed the survival and success rates of 37 titanium-zirconia tissue-level implants placed in a cohort of diabetic patients consecutively treated at a single center. 100% of the implants achieved successful integration. Radiographic analysis confirmed stability of peri-implant bone levels with no evidence of bone loss in the first year of function.

A cross-sectional analysis of the glycemic lev-

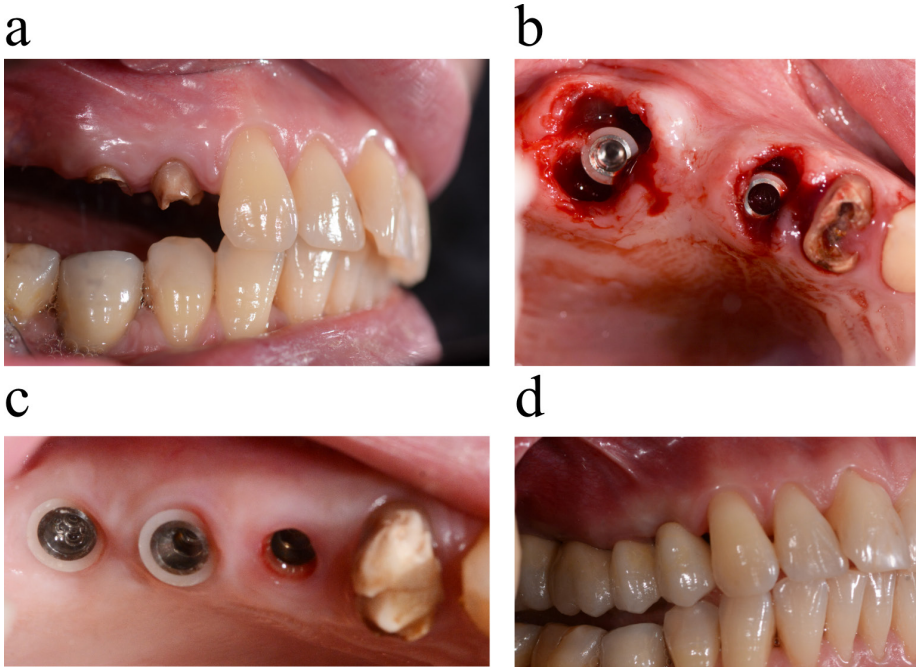

Fig.1 – Model case for the technique. A) The patient required implant-retained rehabilitation of the posterior maxilla; B) Implants were placed both in healed sites and in extraction sockets and then they were immediately loaded; C) Intraoral photograph three months after loading documenting healthy soft tissue; D) Intraoral photograph documenting the successful integration of the rehabilitation two years after loading.

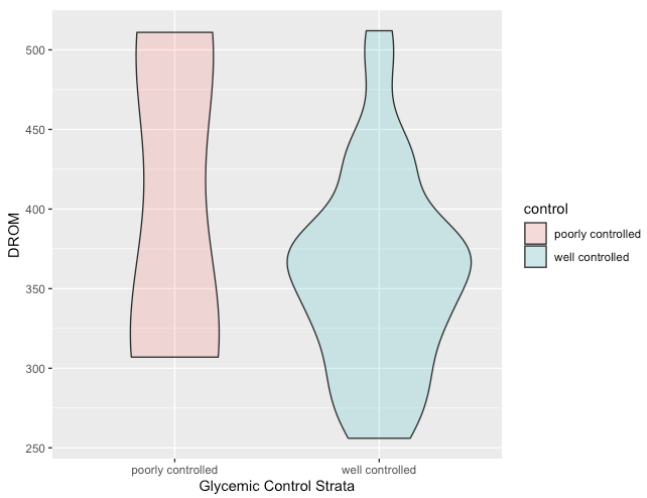

Fig. 2 – Violin plot showing the Kernel density distribution of the systemic reactive oxygen species (dROMs) in U CARR among well controlled and poor controlled patients.

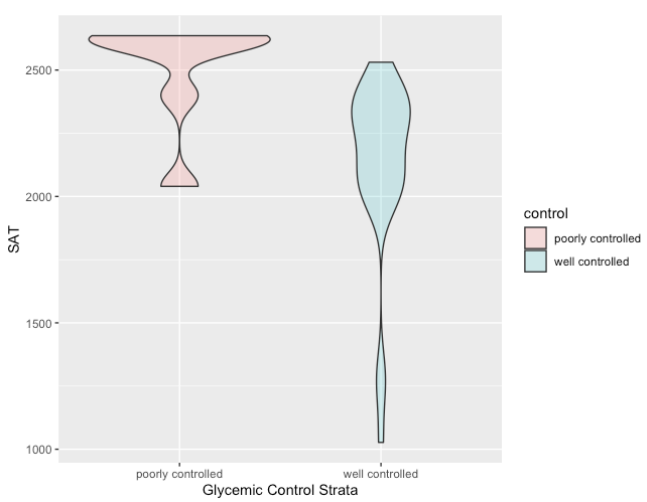

Fig. 3 – Violin plot showing the Kernel density distribution of the salivary oxidative stress (SAT) in U CARR among well controlled and poor controlled patients.

els and oxidative stress status has been pursued in order to investigate the distribution of the average values of those variables around the mean of the population and among different patients' strata.

The stratified analysis suggested that the salivary level of oxidative stress is more specific as an index to describe the patients' oral health. In fact, despite all patients presented high level of systemic oxidative stress - which is the standard finding for T2DM cases, most of them (91.9%) showed an optimal salivary antioxidant potential, with no signs of local inflammation. This finding is readily explained by the fact that, at the very beginning, all patients had been included in the surgery only if not presenting acute inflammation or other gross dental disorders. Furthermore, patients were included in a strict professional hygiene regimen which involved at least 3 sessions per year and reiterate reinforcement of instructions for proper domestic care. Therefore, the titanium-zirconia tissue level implant may provide predictable results in diabetic patients with varying levels of glycemic control and systemic oxidative stress, as long as the general oral health is preserved.

A marked increase in salivary antioxidants concentration, which corroborates earlier findings [21-22], was observed in the saliva of diabetic patients in the present study. The SAT test showed a positive correlation with blood glucose. Uncontrolled diabetic patients had higher SAT levels, suggesting its association with severity of this disease. This supports the compensatory antioxidant defense by antioxidants present in saliva.

In the recent study by Shirzaiy and co-workers, the authors evaluated the correlation between salivary lipid peroxidation and glycemic control [23]. The authors found that diabetic patients had more reactive salivary antioxidants than the healthy control group.

Different clinical trials have shown implant survival rates of up to 100% among patients with well-controlled diabetes [24-26]. It means that diabetic patients are suitable candidates for dental implant therapy and can reach high implant survival and success rates similarly to healthy subjects, provided that they are well controlled in both their glycemic and oral health status [27].

The stability of the marginal bone levels might be determined by different factors, one of these being the apico-coronal location of the implant-abutment interface, as this is responsible for the circumferential inflammatory infiltrate at the gap [28]. Davarpanah observed that bone resorption around the implants placed at the supra-crestal level was less than that of the implants placed at the crestal level, as when the first thread is moved in a coronal direction, the implant platform is moved upward as well [29]. Tissue-level implants displace the chronic inflammation in a coronal position, far from the bone, and elicit the establishment of a firm, thick amount of protective connective tissue around the implant [30-31]. This is even truer if the trangingival portion of the implant is made out of zirconia, which has been proven to be a highly biocompatible material, with great affinity for gingival fibroblasts [32-33]. Therefore, titanium-zirconia one-piece implants might be considered as a valid implant design in the diabetic patient, which is at higher risk for infective-inflammatory complications. A recent cohort study by Latimer and co-workers displayed similar findings, as HbA1c levels did not compromise 1-year survival or success rates in diabetic patients receiving Ti-Zr implants [34].

One limitation of the present study is that tobacco smokers and subjects with systemic diseases other than type-2 diabetes, as well as patients presenting acute periodontal or endodontic inflammation were excluded. Limitations of this study include the short-term follow-up that does not capture increased risk for peri-implantitis or compromised long-term survival. Then, oxidative stress is a complex mechanism, with many situations affecting it. In the present study, oxidative stress measures were not adjusted for inflammation or obesity. Further studies with greater sample size, longer follow-up, a control group, and the report of body mass index and leucocyte count are recommended to corroborate the present findings.

Risk stratification enables oral health providers to identify the right level of care and

therapeutic strategies for distinct subgroups of patients. In this case, it is the process of assigning a risk status to diabetic patients, then using this information to direct care and improve overall health outcomes.
Segmenting the diabetic population according to health care needs allows the clinician to target the existing resources more efficiently and at a lower biologic/economic cost for the patient.
Assessment of salivary antioxidants could be a non-invasive beneficial procedure for monitoring the effectiveness of treatment of diabetes as well as a fast chair-side screening for pre-diabetes and a way to route patients to the appropriate treatment plan.

Abbreviations

T2DM: diabetes mellitus type 2; fBIC: first bone-to-implant contact; MBL: marginal bone level; SRs and CSRs: survival and cumulative success rates; HbA1c: Hemoglobin A1c; d-ROMs: derived reactive oxygen metabolites; SAT: salivary antioxidant test.

Acknowledgements

Not applicable.

Funding

No funding was received for this study.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
The present study was approved by the CHLN and CAML Lisbon Ethical Committee with identity number 350/18. . Patients who were willing to participate were asked to sign a written informed consent, in which scopes and methods of the current protocol were detailed.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

FIGURE /LEGEND

Fig1. Model case for the technique. A) The patient required implant-retained rehabilitation of the posterior maxilla; B) Implants were placed both in healed sites and in extraction sockets and then they were immediately loaded; C) Intraoral photograph three months after loading documenting healthy soft tissue; D) Intraoral photograph documenting the successful integration of the rehabilitation two years after loading.
Fig.2. Violin plot showing the Kernel density distribution of the systemic reactive oxygen species (dROMs) in U CARR among well controlled and poor controlled patients.
Fig.3. Violin plot showing the Kernel density distribution of the salivary oxidative stress (SAT) in U CARR among well controlled and poor controlled patients.

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