

Implant Survival in Renal-Transplanted Patients: A Prospective Long-Term Study

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The present study aims to assess the feasibility of implant rehabilitation in kidney-transplanted patients. Patients with kidney transplantation included in periodontal supportive care and at least one year of dialysis with mono- or partial edentulism were eligible for this study. Histomorphometric evaluation of the harvested bone was matched with radiological bone assessment. Implant stability was also monitored with resonance frequency analysis and insertion torque value. Fixed cemented prostheses have been delivered after conventional loading protocol. Supportive periodontal therapy has been administered. Eleven patients (9 males and 2 females) were included. The mean age was 58.1 ± 9.9 years. A total of 17 implants were inserted and analyzed. Mean ITV was 39.3 ± 23.8 Ncm. The mean primary stability (implant stability quotient) at T0 was 71.7 ± 10.5 , whereas the mean secondary stability at T1 was 73.0 ± 7.3 . The minimum follow-up was 62 months, with a maximum of 84 months (7 years) reached by 4 patients. Fourteen out of 15 implants were in function at a 5-year follow-up (survival rate: 93.3%). Two implants showed peri-implantitis. Seventeen bone samples were collected (13 in the mandible and 4 in the maxilla). The mean percentage of marrow spaces and lamellar bone was 41.6% and 58.4%, respectively. Class 3, according to Misch classification, was found as the mean value of radiological bone density. It can be concluded that implant-supported rehabilitation in kidney-transplanted patients is possible. Adequate periodontal maintenance allows implant rehabilitation in kidney-transplanted patients with long-term sufficient survival rates.

Key Words: renal transplant, kidney transplant, dental implants, dental treatment, immunosuppression

INTRODUCTION

Renal transplantation is a widespread surgical procedure, mainly adopted in the case of end-stage renal disease (ESRD) due to chronic kidney insufficiency in the advanced state or congenital primary renal dysfunction. The aim is the achievement of a physiological function, and this intervention is often associated with hemodialysis and immunosuppressive therapy.

A total of 35,990 kidney transplantations were performed in Italy from 2000 to 2019, according to a report published by the Italian National Transplant Center in 2021. Based on these numbers, it is evident that there is a growing request for dental care and, consequently, for implant-supported rehabilitation in patients who underwent this surgical intervention.

Oral healthcare is fundamental before solid organ transplantation, elimination of infective foci is mandatory, and tooth extraction is often necessary.^{1,2} Periodontal disease and endodontic issues are potential sources of infection, causing alterations of the oral microbiota that can affect the prognosis of

the organ transplant recipient. The achievement of periodontal health should be considered an essential goal, and its maintenance is fundamental from a systemic point of view by lowering the overall bacterial load. Gram-negative bacteria are the most frequent cause of post-transplant septicemia, according to Anderson et al. The oral cavity represents an important reservoir for these microorganisms, associated with periapical inflammatory lesions of endodontic origin.³

On the other side, clinicians are concerned about implant surgery in transplanted patients since kidneys, as is well understood, play a pivotal role in bone metabolism, specifically in calcium-phosphate homeostasis. Renal end-stage disease determines alterations in bone mineralization and a higher fracture risk.

According to the literature, bone metabolism and wound healing may be altered in patients receiving organ transplantation, and this is mainly due to immunosuppression, an unavoidable condition of post-transplant medications.^{4,5} Renal transplantation is, in fact, followed by immunosuppressive therapy, which can lead to the inhibition of osteoblast function and osteogenesis and a consequent reduction of bone-to-implant contact, according to some in vitro studies.^{6,7} Moreover, oral lesions such as gingival overgrowth, candidiasis, coated tongue, and leukoplakia⁸ are connected to such medications, as highlighted by Kaswan and coworkers.

In 2015, Nappalli and Lingappa defined the main oral complications in transplanted patients, dividing them into infective

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and noninfective.⁹ Infective complications are mainly herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus infections; candidiasis; aspergillosis; cryptococcosis; mucormycosis; and blastomycosis. Noninfective complications are represented by neoplasms, squamous cell carcinoma, lymphoma, Kaposi's sarcoma, graft-versus-host disease, oral mucositis, salivary gland dysfunction, and developmental defects. Patients suffering from ESRD usually undergo an undefined period of hemodialysis before kidney transplantation.

Hemodialysis is a medical therapy aiming to restore renal functionality in subjects with severe renal insufficiency. Its function is to filter the blood drawn from the patient through a semi-permeable membrane before reinfusing it. Renal transplantation, although solving insufficiency, may lead to complications, such as acute or late rejection, defined with a threshold of 3–4 months after surgical intervention. Therefore, kidney-transplanted patients can be considered a hard task for the dental care team due to altered tissue response to treatments and susceptibility to infections. Implant therapy, which represents an elective surgery, may be considered to restore both esthetics and function even in such patients. However, to the authors' knowledge, only a few studies analyzed the outcome of implant-supported rehabilitation in patients who underwent kidney transplantation and hemodialysis,^{10,11} where medical history may have a role in the osseointegration process.

Therefore, this long-term prospective study aims to evaluate clinical outcomes of implant therapy in patients with past hemodialysis and kidney transplantation up to 7-year follow-up.

MATERIALS AND METHODS

This prospective study analyzed implants placed between November 2014 and May 2018 at the University's Maxillofacial Surgery and Stomatology Clinic. The enrolled patients were thoroughly informed about the study protocol, related risks, and therapeutic alternatives and signed a written informed consent. All patients underwent hemodialysis (at least for one year) and kidney transplantation before entering the present study.

This study was conducted according to the Helsinki Declaration and the current laws and regulations on observational studies and received authorization from the relevant regional Ethical Committee (n° 34/2014). This protocol has been registered in the public database of clinical studies (clinicaltrials.gov identification number NCT02513602).

INCLUSION CRITERIA

All the enrolled patients met the following inclusion criteria:

- patients with mono- or partial edentulism (maximum: 3 adjacent missing teeth) requiring an implant-supported rehabilitation;
- presence of natural teeth or fixed prosthesis in the opposing arch;
- at least 1 year of previous hemodialysis or peritoneal dialysis;
- permanent immunosuppressive therapy (after renal transplant);
- sufficient bone volume to allow implant placement without regenerative surgery (minimum bone crest width: 6 mm; minimum bone crest height: 7 mm);
- periodontal health (absence of pockets with probing depth >4 mm; total mouth bleeding score <10%).¹²

EXCLUSION CRITERIA

Patients were excluded from the study if one or more of these conditions were present:

- immediate or early implant placement¹³ (less than 4 months elapsed from tooth extraction);
- patients <18 years old;
- heavy smokers (>10 cigarettes/d).

OPERATIVE PROCEDURE

Preradiological phase: periodontal chart

Patients who met inclusion criteria underwent a complete periodontal evaluation. If necessary, patients were treated with periodontal causal therapy and then re-evaluated after 30 days. The following periodontal values were assessed using a standard periodontal probe (PCP-12, Hu-Friedy, Chicago, IL, USA): plaque index (PI), bleeding on probing (BoP), and probing pocket depth (PPD). Further periodontal values were considered: gingival recessions, tooth mobility, and furcation involvement. Oral hygiene habits were monitored until acceptable BoP and PI values (<25%) were reached¹⁴. All the patients were already following a maintenance program, with personalized recall timing according to their periodontal conditions. One week before the surgical procedure, patients underwent a professional deplaquing session to lower the bacterial load.

Radiological phase: CBCT

After performing polyvinylsiloxane impressions, resin dental casts were produced, and a radiologic resin template was manufactured based on the diagnostic wax-up (RealGUIDE, 3Diemme, Como, Italy). Cone beam computerized tomography (CBCT) was performed with a standardized 15 × 12 field of view (FOV) and the same radiological device for all patients (NewTom VGI, Cefla, Imola, Italy). Peri-implant bone density was assessed on CBCT imaging by a single operator (FB), according to Vercellotti and Vercellotti classification considering cortical (1 mm, 2 mm, 3 mm) and trabecular (1 = low, 2 = medium, 3 = high) bone, and to Misch classification.^{15,16}

Implant planning

Virtual implant planning was performed by a single operator (FB) using dedicated software (3Diagnosys, 3Diemme, Como, Italy). Planning was performed by simulating 1 mm subcrestal insertion of conical connection, platform-switched implants (GTB, Advan Implantology, Amaro, Italy), according to the surgical protocol suggested by the manufacturer. These implants are characterized by conical connection with platform switching.

The selected implants, presenting cylindrical-conical macrogeometry and moderately rough surface, had a diameter of 3.6 or 4.3 mm, and a length of 7.5 – 9 – 10.5 – 12 mm.

Surgical phase (T0)

One hour before surgical intervention, patients received antibiotic prophylaxis (amoxicillin 2 g, or clarithromycin 500 mg if allergic). Intra- and extraoral disinfection with povidone-iodine

10% solution (Betadine, Viatrix, Canonsburg, PA, USA) was performed. Local anesthesia was performed (mepivacaine hydrochloride 20mg/mL + adrenaline 1:100'000, Optocain, Molteni Dental, Milano, Italy). After reflecting a full-thickness flap, the dental-supported resin surgical template was positioned, and implant sites were prepared using a trephine bur with an inner diameter of 2.5 mm and an external diameter of 3.0 mm (#2982.Y0.25, DenTag, Maniago, Italy). Harvested bone samples were immediately placed in a 10% formalin-buffered solution. After implant placement, insertional torque value (ITV)^{15,16} was recorded with a dedicated surgical motor (Elcomed, W&H, Bürmoos, Austria). Four implant stability quotient (ISQ) values (mesial, distal, buccal, and lingual) were measured in duplicate with a resonance frequency analysis (RFA) device (Osstell Mentor, Osstell, Göteborg, Sweden) and a dedicated magnetic transducer (Smartpeg #57, Osstell, Göteborg, Sweden), screwed to the implant. A 1-mm-high cover screw was inserted, and flaps were sutured with polypropylene 4-0.¹⁷ A periapical radiograph with a Rinn holder and a custom polyvinylsiloxane jig was performed immediately after implant placement. Each following periapical radiograph was performed using the same procedure.

Patients received antibiotic therapy (amoxicillin 2 g/d or clarithromycin 500 mg twice daily for 6 days), and chlorhexidine 0.12% rinses were prescribed (twice daily for 10 days).

HISTOMORPHOMETRIC ANALYSIS

Sample harvesting and biopsies management

Samples were fixed for at least 24 hours in 10% neutral-buffered formalin and then dehydrated for resin inclusion (London White Resin LWR, Sigma Aldrich, St. Louis, MO, USA). Final slices were stained with toluidine blue and acid fuchsin. Histomorphometric analysis was then performed with the definition of the following parameters: compact lamellar bone (CL), spongy lamellar bone (SL), marrow spaces (MS), and bone volume/total volume (BV/TV).

POSTSURGICAL PHASE AND HEALING ABUTMENT POSITIONING

Sutures were removed 1 week after implant placement, whereas healing abutments were positioned after 3–5 and 6–10 months for mandibular and maxillary implants, respectively (T1). Secondary stability was evaluated at the second stage of surgery using ISQ measurement as previously described.

PROSTHETIC PHASE

One month after suture removal, impressions were taken using polyvinylsiloxane, and metal-composite crowns were manufactured and fixed with zinc-oxide-eugenol cement.

Occlusion and emergency profiles were checked, and cement remnants were carefully removed.

All patients continued the periodontal recall program as previously attended.

IMPLANT HEALTH

Peri-implant health was evaluated considering plaque index (PI), bleeding on probing (BoP), and pocket probing depth

(PPD). Each implant site received a label identifying its health status.¹⁸

- S: success, healthy:
 - absence of clinical signs of inflammation;
 - absence of bleeding/suppurative on gentle probing;
 - no increase in probing depth compared to previous examinations;
 - no evidence of bone loss.
- M: mucositis:
 - bleeding and/or suppurative on gentle probing;
 - no evidence of bone loss.
- P: peri-implantitis:
 - bleeding and/or suppurative on gentle probing;
 - increased probing depth compared to previous examinations;
 - evidence of bone loss.
- F: failure

RESULTS

A total of 11 patients (9 males and 2 females) were included in this study. The mean age was 58.1 ± 9.9 years. A total of 17 implants were inserted and analyzed. Bone density evaluated according to Misch classification and bone quality evaluated according to Vercellotti & Vercellotti classification are reported in Table 1. The same table reported a bone density evaluation for each implant site based on CBCT gray values.

ITV and ISQ

Mean ITV was 39.3 ± 23.8 Ncm. The mean primary stability (ISQ) at T0 was 71.7 ± 10.5 , whereas the mean secondary stability at T1 was 73.0 ± 7.3 . Complete ISQ and ITV values are reported in Figure.

CLINICAL OUTCOMES

Peri-implant health was monitored through clinical and radiographic analyses (Table 2). The minimum follow-up, excluding a single case due to patient death 9 months after prosthesis delivery (TS01), was 62 months, with a maximum of 84 months (7 years) reached by 4 patients. Periodontal and peri-implant maintenance protocol is still in progress for each enrolled patient. Fourteen out of 15 implants were satisfactorily in function at 5-year follow-up (survival rate: 93.3%).

One implant (TS10B) developed peri-implantitis 11 months after implant placement and was removed and immediately replaced after an accurate curettage of the surgical site. At 30 months from prosthetic loading, the new implant (not included in the study) is successfully in function.

One implant (TS04) developed peri-implantitis 3.25 years after its placement. The fixture was treated with resective surgery: after satisfactory soft tissue healing, a new abutment and prosthetic crown were delivered.

HISTOMORPHOMETRIC ANALYSIS

Seventeen bone samples were collected (14 in the mandible and 3 in the maxilla). Mean percentage of marrow spaces and lamellar

Patient	Implant Site	Gray Value	SD	Misch	V&V Cortical	V&V Trabecular
TS01A	46	861.774	312.655	3	2	1
TS01B	36	808.473	331.944	3	3	1
TS02A	34	982.166	363.916	2	1	3
TS02B	35	1030.740	265.730	2	1	3
TS03	36	611.747	148.346	4	1	1
TS04	46	394.389	134.382	3	1	1
TS05A	46	381.284	207.768	4	1	1
TS05B	36	383.844	196.117	4	2	1
TS06A	26	323.934	212.584	3	1	1
TS06B	46	306.026	188.684	4	1	2
TS07A	46	681.596	214.784	3	0	2
TS07B	47	826.399	178.742	3	0	2
TS08	36	267.687	364.442	3	2	1
TS09	22	558.319	221.652	3	1	3
TS10A	24	457.391	134.078	4	1	3
TS10B	46	628.374	252.34	3	1	2
TS11	36	387.989	289.8	3	1	3
Mean		581.890	236.351	3.18	1.18	1.82
Median		558,319	214,784	3	1	1,5
Mode		/	/	3	1	1

*SD indicates standard deviation; V&V, Vercellotti & Vercellotti. Letters A, B on the same ID mean more than one implant in the same patient.

bone was 41.6% and 58.4%, respectively. Complete results for CL, SL, total lamellar bone (total L), and MS are listed in Table 3. BV/TV can be derived from total L in respect to the whole amount.

DISCUSSION

Renal transplanted patients present anomalies of bone metabolism and bone structure quality, as a result of dialysis and immunosuppressive therapy. Chronic renal insufficiency can lead to a particular bone pathology (renal osteodystrophy), which is part of a wider group of pathologies (mineral and bone disorders in chronic kidney disease). As previously

mentioned, kidneys play a fundamental role in the regulation of calcium-phosphate metabolism, and their malfunction may lead to the reduction of hematic calcitriol with consequent higher parathyroid hormone secretion. These events reduce bone density, enhancing the risk of skeletal fragility and fracture.

Renal transplant is the main therapy adopted to solve ESRD, with consequent improvement of bone metabolism; however, some metabolic disorders may persist after transplantation, mainly in the first two years. Moreover, transplanted patients usually receive high dosages of corticosteroids, which interfere with calcium-phosphate homeostasis, therefore enhancing osteoclastic activity and bone resorption phenomena.

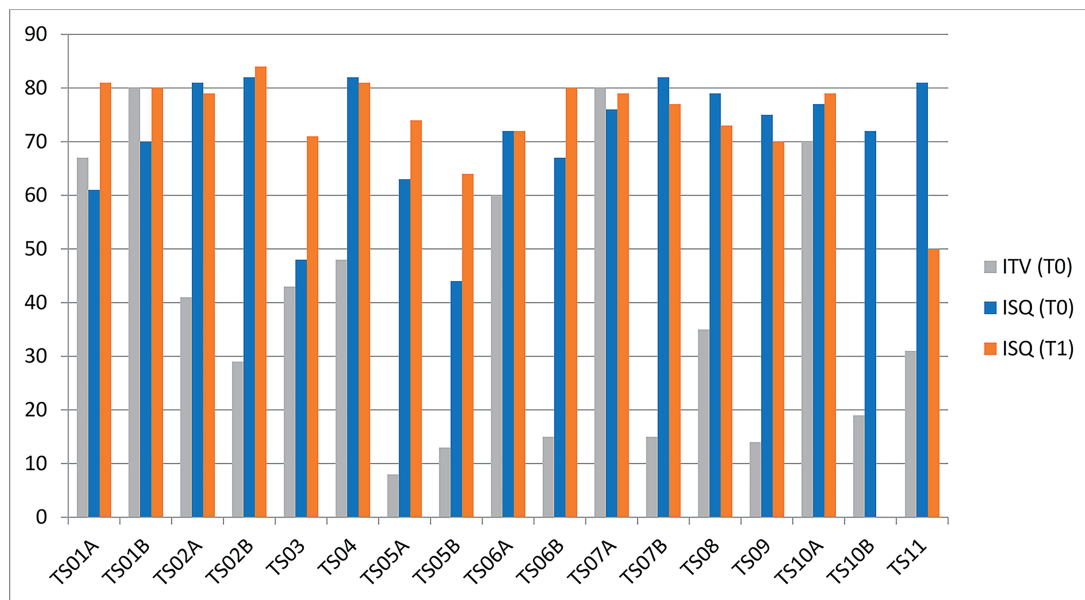


FIGURE. ISQ at implant placement (T0) and at 3-5 months (T1); Insertional Torque Value (ITV) at implant placement (T0).

TABLE 2

Implant characteristics and health status at different follow-ups*

Patient	Implant site	Diameter (mm)	Length (mm)	3 mo	6 mo	12 mo	18 mo	24 mo	36 mo	48 mo	60 months	72 months	84 months
TS01A	46	3.6	9	H	H	/	/	/	/	/	/	/	/
TS01B	36	3.6	9	H	H	/	/	/	/	/	/	/	/
TS02A	34	3.6	10.5	H	H	H	H	H	H	H	H	H	H
TS02B	35	3.6	10.5	H	H	H	H	H	H	H	H	H	H
TS03	36	3.6	9	H	H	H	H	H	H	H	H	H	H
TS04	46	4.3	9	H	H	H	H	P	P	H	H	H	H
TS05A	46	3.6	9	H	H	H	H	H	H	H	H	/	/
TS05B	36	3.6	7.5	H	H	H	H	H	H	H	H	/	/
TS06A	26	3.6	7.5	H	H	H	H	H	H	H	H		
TS06B	46	3.6	9	H	H	H	H	H	H	H	H		
TS07A	46	3.6	9	H	H	H	H	H	H	H	H		
TS07B	47	3.6	7.5	H	H	H	H	H	H	H	H		
TS08	36	3.6	6	H	H	H	H	H	H	H	H		
TS09	22	3.6	10.5	H	H	H	H	H	H	H	H		
TS10A	24	3.6	7.5	H	H	H	H	H	H	H	H		
TS10B	46	3.6	10.5	H	H	F							
TS11	36	4.3	7.5	H	H	H	H	H	H	H	H		

*Empty box indicates the patient has not reached the follow-up interval yet; F, failure; H, healthy; P, peri-implantitis; "/", the patients dropped out. Letters A, B on the same ID mean more than one implant in the same patient.

For these reasons, implant-supported rehabilitation in renal transplanted patients is still a debated issue and there is no evidence of specific surgical protocols or guidelines. The present study showed that, with an accurate anamnestic evaluation, a careful patient selection (especially from a periodontal point of view) and the application of a strict surgical protocol, implant-supported rehabilitation may represent a feasible option (93.3% survival rate after 5 years of prosthetic loading). Inclusion of these patients in a maintenance program is of utmost importance to ensure long-term success and longevity of dental implants. Instructions to a correct domiciliary oral hygiene should be coupled with continuous motivation, underlining that

periodontal health can indeed have a positive impact on the general health and well-being of renal transplanted patients, as stated by many authors.^{19,20}

Nonetheless, some biological complications occurred during the follow-up period. One implant was lost for peri-implantitis during the first year after prosthetic loading (1 out of 15 implants, 6.7% failure rate). A second implant was diagnosed with peri-implantitis 3.25 years after prosthesis delivery and successfully treated with resective therapy. Incidence of peri-implantitis was 13.3%, with a follow-up ranging from 5 to 7 years. Both the failure rate and incidence of peri-implantitis recorded in the present study are higher than the results reported in a recent prospective study by Hernández and coworkers (2019).²¹ This investigation, including 79 implants placed in renal transplanted patients followed from 84 to 192 months after loading, reported 100% implant survival rate and 5.1% peri-implantitis incidence. These different outcomes should be compared with caution due to the small sample of the present study, in which the occurrence of a single event may heavily impact its prevalence.

In the present study, mean bone density, according to Misch classification, was D3 in more than 70% of implant sites, with 1 mm of cortical bone in 63% of cases (according to Vercellotti & Vercellotti classification), and a medium/high trabecular space value (=2). Eleven out of 15 implants have been positioned in the posterior mandible: in healthy populations, type 2 and 3, according to Misch classification, should be expected in this area.¹⁶ A lower bone density in the present sample may be justified by different grades of osteopenia/osteoporosis that characterize the population included in this study. Nonetheless, the mean insertion torque recorded in the present study was 39.3 ± 23.8 Ncm: if 30 Ncm is generally accepted as a threshold for immediate loading protocol, most of the implants inserted in the present study could have been treated that way.²²

TABLE 3

Histomorphometric analysis*

Patient	Site	CL	SL	TOTAL L	MS
TS01A	46	90.00%	0.00%	90.00%	10.00%
TS01B	36	65.00%	7.00%	72.00%	28.00%
TS02A	34	32.00%	23.00%	55.00%	45.00%
TS02B	35	83.00%	0.00%	83.00%	17.00%
TS03	36	27.00%	46.00%	73.00%	27.00%
TS04	46	0.00%	61.00%	61.00%	39.00%
TS05A	46	2.00%	38.00%	40.00%	60.00%
TS05B	36	19.00%	21.00%	40.00%	60.00%
TS06A	26	10.40%	37.40%	47.80%	52.20%
TS06B	46	5.62%	51.16%	56.78%	43.22%
TS07A	46	2.02%	46.52%	48.54%	51.46%
TS07B	47	10.18%	52.35%	62.53%	37.47%
TS08	36	23.96%	31.88%	55.84%	44.17%
TS09	22	22.10%	25.50%	47.60%	52.40%
TS10A	24	9.50%	54.73%	64.23%	35.77%
TS10B	46	17.89%	31.07%	48.96%	51.04%
TS11	36	12.80%	34.36%	47.16%	52.84%
Mean		25.44%	33.00%	58.44%	41.56%

*CL indicates compact lamellar bone; L, lamellar bone; MS, marrow spaces; SL, spongy lamellar bone.

The mean implant stability quotient was 71.7 ± 10.5 and 73.0 ± 7.3 at T0 and T1, respectively. Similar to ITV data, ISQ values are also comparable with data recorded in the general population.^{23–25} It should be noted that, considering the subcrestal implant placement and the mean cortical thickness assessed in the preoperative CBCT scans (≈ 1 mm), primary stability was mainly obtained by implant anchorage to the cancellous bone.

Gray values assessment resulted in difficult interpretation given the broad range of results and high standard deviation (581.9 ± 236.4 ; range: 267.7–1030.7), despite the attempts made to standardize the procedure to reduce variability (same CBCT device, same FOV, same operator). Alveolar bone morphology of the included patients could justify these variations for the presence of mixed radiolucent and denser areas. Furthermore, comparison with other studies is not feasible, given the known differences among CBCT/CT devices and different FOVs.²³

Histomorphometric evaluation brings information about the native bone of renal transplanted patients, which is potentially scarcely mineralized. Mean lamellar bone was $58.4 \pm 14.1\%$, whereas marrow spaces were $41.6 \pm 13.9\%$. These data confirmed that the mean bone quality of the retrieved samples was D3 according to Trisi and Rao, who indicated a mean bone percentage of $59.6 \pm 19.6\%$ (range: 30%–82%) for D3 quality.²⁴ Despite the expected poor bone quality, The BV/TV ratio ($58.3 \pm 14.1\%$) of samples collected in the present study resulted at least higher than the mean BV/TV of regenerated bone.^{25–27} However, a meaningful comparison between histomorphometric data of kidney-transplanted patients and healthy subjects cannot be made due to the paucity of literature data. Dias and coworkers (2015) aimed to assess the comparability between microCT and histomorphometry. Forty-four human native bone samples were used for this purpose, but without providing details about the sites of harvesting. Mean BV/TV of pristine, healed alveolar bone was $51.7 \pm 16.3\%$ (range: 17.6–82.9).²⁸ Reported data are in line with the results of the present study ($58.3 \pm 14.1\%$; range: 40.0–90.0).

The present study was based on a long-standing collaboration between the dental and nephrology departments, where candidates for a kidney transplant, transplanted, and dialytic patients are inserted in a specific periodontal protocol. This study highlighted how long-term outcomes of implant-supported rehabilitation in these patients may be improved if periodontal health is maintained. Besides the long follow-up, unfortunately the small numerosity of the present study hampers a generalization of the findings. This limitation should be kept in mind in exporting the present results.

However, basing on the data from the present analysis, no significant differences in terms of bone quality were detected between renal transplanted patients and healthy patients. To date, implant-supported rehabilitation seems a feasible treatment in these subjects, if accompanied by a rigid protocol of oral hygiene maintenance.

CONCLUSIONS

Based on the results, a key role in implant-supported rehabilitation is an accurate choice of patients and the adoption of correct diagnostic and therapeutic protocols. The main limitation of this study is the low number of enrolled patients,

mostly due to their suspicion of the surgical procedure that is believed not to be vital for patients' health. Therefore, it can be concluded that implant-supported rehabilitation in kidney-transplanted patients is possible. Further studies are needed to evaluate long-term clinical and radiographic values.

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NOTES

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