



Osseointegration of Dental Implants in Organ Transplant Patients Undergoing Chronic Immunosuppressive Therapy

Rafał Radzewski, MD, DDS* and Krzysztof Osmola, MD, DDS, PhD†

Thanks to the advancement in transplantology, the number of patients with organ transplants in an overall population has been increasing. In 2015, there were more than 3200 transplantations in Europe, among which 61.46% concerned kidneys and 23.52% liver.¹ A significant group of those patients requires dental rehabilitation; since in the course of preparations for the procedure, extraction of numerous teeth is often enforced by the need to sanitize oral cavity.² This group encompasses very young people and mature patients.³ The issue of dental rehabilitation is very important for everyone, although among elderly patients other, sometimes more serious difficulties may be encountered. What is crucial is the fact that survival time of the patients after successful transplantation has been constantly on the increase. Many patients live more than 20 years after transplantation procedures; consequently, the question of life quality related to appropriate functioning of their stomatognathic system is absolutely crucial.

Introduction: The depressive impact of immunosuppressive medications used by patients after organ transplantations is commonly known and well proven. The aim of research is the assessment of functional and esthetic results of implant-toprosthesis treatment in patients subject to immunosuppressive treatment after organ transplants.

Materials and Methods: The study encompassed a group of 21 patients in the course of maintenance immunosuppression after transplantation procedures, in whom altogether 24 implants were inserted. The control group comprised 15 people with 15 implants in place. The research protocol assumed replacing a single missing tooth with a titanium implant. After 4 months, a prosthetic reconstruction in the form of a single crown was performed. After 24 months, the preliminary assessment of treatment

results was attempted. The measured parameter was crestal bone level (CBL). The mechanical assessment was performed by measuring the torque indispensable to locate the implant and by an objective measurement of implant stability.

Results: The basic measured parameter of CBL median in the experimental group and in the control group amounted to 0.325 mm (min 0–max 0.95) and 0.5 mm (min 0.15–max 1.8), respectively. The comparison of CBL medians revealed lack of significant differences between the experimental group and the control group ($P = 0.089$).

Conclusion: Patients with organ transplants can safely and effectively undergo dental implant treatment. (*Implant Dent* 2019;28:447–454)

Key Words: crestal bone level, solid-organ transplantation, endosseous implant, immunosuppression

The use of titanium implants is considered the best method of replacing the missing teeth. However, the depressive impact of immunosuppressive medications used by patients after organ transplantations till the end of their lives is commonly known and well proven.^{4,5} For many years, it has been considered that immunosuppression is an absolute contraindication to undertake the treatment with the use of dental implants.^{6,7} What is more, all surgical procedures

performed on these patients are associated with a higher risk of infection. This undoubtedly has got some bearing on the potential hazard of dental treatment failure and may influence the overall health condition of the patient.

Few studies conducted on animals provide inconclusive evidence as to the impact of immunosuppressive medications on the healing bone around dental implants.^{8–12} The case studies on human patients reveal that

*PhD Student, Department of Maxillofacial Surgery, Poznan University of Medical Sciences, Poznan, Poland.
†Professor, Department of Maxillofacial Surgery, Poznan University of Medical Sciences, Poznan, Poland.

Reprint requests and correspondence to: Rafał Radzewski, MD, DDS, Ethica Dental Clinic, Zbąszyńska 32/102, 60-397 Poznań, Poland, Phone: +48500085651, Fax: +48616711040, E-mail: rafal.radzewski@gmail.com

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irrespective of unfavorable influence on bone structures, the implants do not have a negative impact on implant stabilization.^{13–16} So far, there have been 2 studies assessing the effect of immunosuppressive treatment on the dental implants in patients with organ transplants (heart and liver).^{17,18} Neither of them indicates any negative impact on dental implants.

Aim

The aim of our research is the assessment of functional and esthetic results of implantoprosthodontic dental treatment in patients subject to immunosuppressive treatment after organ transplants. Moreover, the authors decided to examine whether in patients undergoing immunosuppression there occurs bone loss, what is its scale, and whether particular immunosuppressive medications differ as to their effect on osseointegration.

MATERIALS AND METHODS

The study encompassed a group of 21 patients in the course of maintenance immunosuppression after transplantation procedures, in whom altogether 24 implants were inserted.

The following criteria for patient inclusion in the experimental group were adopted: >25 years of age, at least 1 year after organ transplant, at least one tooth missing with neighboring teeth present, and bone condition (with respect to volume and density) allowing to effect the implantation procedure without the need to perform guided bone regeneration (GBR). The exclusion from the experimental group took place when it was ascertained that the patient had active periodontal disease, substantial occlusion disorders, bone diseases, blood coagulation disorders, untreated dyslipidemia, or was a smoker. The control group comprised 15 people with 15 implants in place. The criteria for inclusion to the control group were lack of serious systemic diseases, more than 25 years of age, at least one tooth missing with neighboring teeth present, and bone condition (with respect to volume and density) allowing to effect the implantation procedure without the need to perform GBR. The

criteria for exclusion from the control group are identical as in the experimental group. In addition, people taking immunosuppressive medications were excluded from the group, irrespective of the indications to use these drugs. In one of the participants of the control group, implant osseointegration was not obtained. The infection, which was the result of the patient's nonobservance of recommendations concerning the antibiotic therapy, leads to implant treatment failure. The patient was excluded from further participation in the experiment; in view of the fact that in his case, it was impossible to take measurements of the selected parameters.

The research protocol assumed replacing a single missing tooth with a titanium dental implant placed subcrestally (Naturactis; ETK, Sallanches, France). In 2 patients, more implants were inserted to compare the effect obtained in the maxilla and in the mandible, and one patient had the implants placed on 2 sides. The surgical procedure was every time preceded and followed by the administration of prophylactic antibiotic agents (orally, doxycycline 0.2 g—2 hours before the operations; 0.1 g, 2 times per day for 5 days, or clindamycin 0.6 g—2 hours before the operations; 0.3 g, 3 times per day for 5 days) and nonsteroidal anti-inflammatory drugs (ketoprofen 0.1 g, 3 times per day for 3 days).

After 4 months, a prosthetic reconstruction in the form of a single crown was performed. The time devoted to osseointegration was extended with respect to the standard span of 3 months, bearing in mind a potentially longer reconstruction process related to the use of immunosuppressive treatment. The research project was scheduled for 4 to 6 treatment months plus 3 years of observation. After 24 months, the preliminary assessment of treatment results was attempted (Fig. 1).

The researchers took into consideration the risk associated with the failure consisting in the lack of implant integration, the need to remove it, and lack of further possibilities of prosthetic reconstruction based on the implant.

Radiological assessment consisted in taking a series of radiovisiographic (RVG) pictures. The first one was taken

on the day of the surgery, the next one after the integration period (4 months), and the subsequent ones every 6 months from the day of implant loading. The measured parameter was crestal bone level (CBL)—the distance from the reference point on the implant to the first visible contact between the bone and implant surface (mesial and distal sides—median). The scale of bone loss was assessed by 2 independent researchers to obtain more objective results (our analysis deploys average values of those measurements) (Fig. 2).

The mechanical assessment was performed in a 2-fold manner: by measuring the torque indispensable to locate the implant (with the use of torque wrench) and by an objective measurement of implant stability (with the use of specialized testing equipment—Osstell). Measurements were performed twice: the first one on the day of implantation and the second one after the integration period (4 months after the operation).

Statistical calculations were executed by means of STATISTICA (data analysis software system), version 12, from StatSoft, Inc. (2014), www.statsoft.com. Analyses were performed based on the assumption of significance level of $P = 0.05$. Owing to the lack of normal distribution, nonparametrical tests were applied.

RESULTS

After 2 years of observation, the results of 35 patients, with altogether 39 implants, were analyzed. The average patient age in the experimental group equaled 39 years (min 31–max 68), and in the control group—43 years (min 22–max 58). Within the control group, 73.3% were women and 26.6% men, whereas in the experimental group, there were 45.8% women and 54.2% men, respectively. The average time elapsing from the transplantation procedure was 5 years (min 2–max 20) (Fig. 3).

Most patients were administered the same immunosuppressive medication, ie, tacrolimus, and the others took cyclosporin, sirolimus, or mycophenolate mofetil, respectively. Twelve patients were taking 2 immunosuppressive medications: mycophenolic mofetil or sirolimus. The



Fig. 1. Intraoral photographs of the patient from the experimental group taken to assess the healing of soft tissues. The view on the day of implant loading and 24 months later. Arrows indicate gum around crowns based on implants.

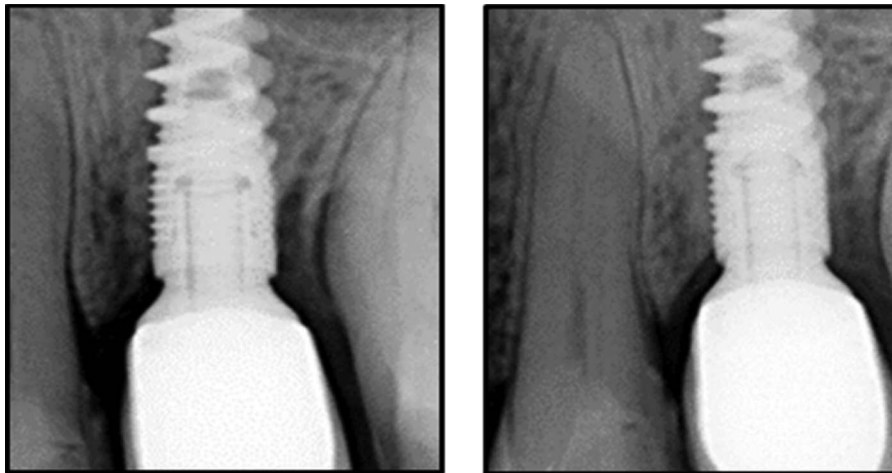


Fig. 2. Radiological assessment of the bone around implants: RVG images taken on the day of implant loading and 24 months later.

therapeutic protocol in the case of 14 patients also included deployment of steroid medications Encorton or Metypred (Fig. 4).

The basic measured parameter of CBL median in the experimental group

and in the control group amounted to 0.325 mm (min 0–max 0.95) and 0.5 mm (min 0.15–max 1.8), respectively. The comparison of CBL medians revealed lack of significant differences between the experimental group and

the control group ($P = 0.089$; *U* Mann-Whitney test with continuity correction).

The next analysis concerned the correlation between the torque and bone loss in the 2 groups. Both in the experimental group ($P = 0.93$) and in the control group ($P = 0.9$), no correlation was found (Spearman's rank correlation coefficient).

Afterward, the correlation between the scale of bone loss and basic immunosuppressive medication taken by the patient, as well as the administration of either 1 or 2 medications or a steroid, was examined (Table 1). The results presented indicate lack of statistically significant difference in the loss of bone around the implant between the patients taking 1 of those 4 medications ($P = 0.212$). The results indicate lack of statistically significant difference in CBL between patients taking steroids and those not taking medications from that group ($P = 0.086$) (Tables 2 and 3).

In the course of statistical analysis, a significant difference in CBL was revealed between patients taking 1 or 2 medications ($P = 0.042$) (Fig. 5).

Implant stability measurement was performed with the use of implant stability quotient (ISQ). In all cases, the obtained values were higher than 55 ISQ, which denotes good or very good implant stability both directly after implantation—ISQ1, and 4 months later—ISQ2 (after the osseointegration period) (Table 4).

Correlation between ISQ1/ISQ2 and CBL was assessed. Neither the analysis of the experimental group or control group nor the analysis of all

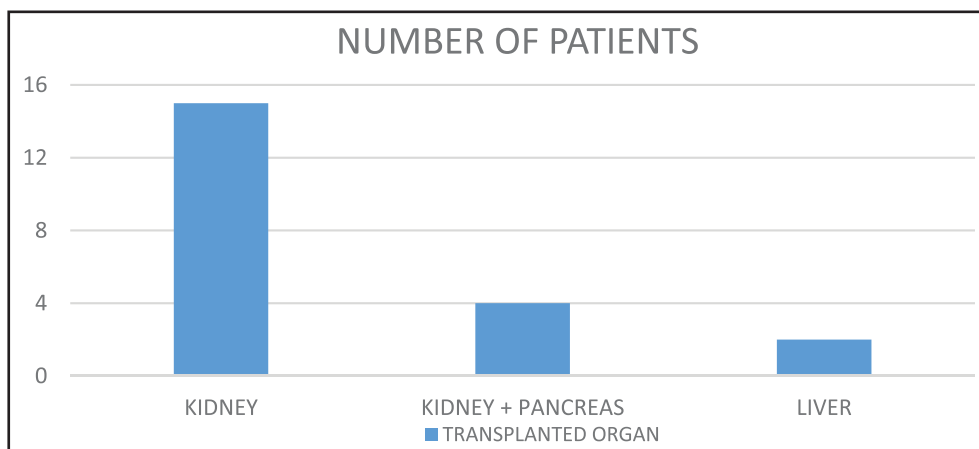


Fig. 3. Analysis of the experimental group: Number of patients with specific transplanted organs.

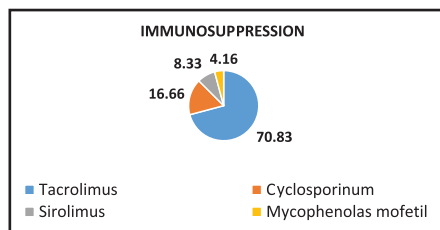


Fig. 4. Analysis of the experimental group: Distribution of patients according to the basic immunosuppressive medication.

DISCUSSION

The issue of dental rehabilitation of patients with organ transplants has not been a subject of too many studies so far.¹⁹ It is generally known that the best way to replace the missing teeth is to use dental implant treatment. While making a decision to choose this method, one must obviously bear in mind the contraindications that might have an impact on the occurrence of complications or

publications by Gu et al from 2011,¹⁴ Gu and Yu,¹⁵ and a study describing 10 organ transplant patients (OTPs) and 10 patients from the control group.^{18,27} The outcomes of all the aforementioned studies have confirmed that there is no impact of immunosuppressive therapy after organ transplantation on the success of dental implant treatment. Substantial limitations of those studies were the considerably low numbers of patients included in the study or a very short observation time. There is also one very interesting case report by Dalla Torre D et al. from 2016.²⁸ Researches prior to implant treatment performed bone augmentation in an organ (liver) transplant patient. After 2 years stable peri-implant conditions and totally integrated bone grafts were presented. Authors claim that not only dental treatment but also bone grafting might be possible in solid organ transplant patients.

The results of our prospective study indicate clearly that there is no difference in the effects of dental implant treatment between patients in the course of immunosuppressive therapy after organ transplantation and the control group of healthy people. None of the patients from either group had any related ailments, and successful osseointegration concerned 100% implants. The basic parameter subject to measurements, CBL median in the experimental group and in the control group, equaled 0.325 mm (min 0–max 0.95) and 0.5 mm (min 0.15–max 1.8), respectively. The results of the research mentioned earlier^{14,15,27} are not substantially different from the outcomes quoted by other authors who assessed bone loss around implants placed in healthy people.^{29,30,31} Gu et al¹⁴ measured the CBL median whose value equaled 1.30 ± 1.3 mm after 36 months in the organ transplant group (OTG), and Montebugnoli et al²⁷ noted lower CBL value in both the experimental and control groups (0.28 ± 0.2 vs 0.42 ± 0.32 mm, respectively), but their observation period was only 3 months. Fransson et al³² obtained the CBL median result at the level of 1.68 ± 1.3 mm after the follow-up period which lasted 60 months. The study of Paredes et al¹⁶ reported that the CBL median equaled (1.53 ± 0.6 mm) in the OTG and (1.64 ± 1.3 mm) in the control group.

Table 1. Correlation Between CBL and the Basic Immunosuppressive Medication

Variable: CBL	Kruskal-Wallis Test			
	Tacrolimus R:10.853	Cyclosporinum R:13.875	Sirolimus R:19.500	Mycophenolas Mofetil R:21.000
Tacrolimus		1.000000	0.611214	0.978855
Cyclosporinum	1.000000		1.000000	1.000000
Sirolimus	0.611214	1.000000		1.000000
Mycophenolas mofetil	0.978855	1.000000	1.000000	

participants without group divisions showed any significant correlations (all *P* values > 0.05). There are no statistically significant differences in ISQ values (*P* = 0.075).

In addition, the authors decided to specify the impact of immunotherapy on the secondary stabilization of implants after 4 months since implantation (ISQ2). The *U* Mann-Whitney test with continuity correction indicated no statistically significant differences (*P* = 0.075) in ISQ values between patients taking steroids (median 74; min 64–max 78) and those not taking steroids (median value 69.5; min 59–max 74.5). A similar result in the form of lack of statistically significant differences (*P* = 0.7) was brought by the comparison between the effect which taking 1 or 2 immunosuppressive medications has on ISQ2 (*P* = 0.7; *U* Mann-Whitney test with continuity correction) (Table 5).

even lead to treatment failure.²⁰ Due to immunocompromised situation of the patient oral infections may put at risk not only the longevity of the implants but also the integrity of the transplanted organ. For many years, the list of these contraindications was extensive: metabolic diseases, osteoporosis, bone diseases, radiotherapy, or immunosuppression.^{21–25} Thanks to the advancement in therapeutic methods and the invention of new medications, we may effectively control the condition of patients. Enhancing the patients' quality of life through the use of implants repeatedly exceeds the risk related to dental implant treatment.²⁶ The study of Montebugnoli et al²⁷ along with the study of Paredes et al¹⁷ are the first 2 prospective studies in the world with the long observation period that were related to the issue.

Hitherto, a few descriptions of single cases with the short follow-up period have been published,¹³ 2

Table 2. Correlation Between CBL and 2 Immunosuppressive Medications

Variable	<i>U</i> Mann-Whitney Test (With Continuity Correction Against the Variable: 1 or 2 Medication(s))				Valid N Group 1	Valid N Group 2
	Rank-Sum Group 1	Rank-Sum Group 2	<i>U</i>	<i>P</i>		
CBL median	147.0000	153.0000	33.00000	0.042131	9	15

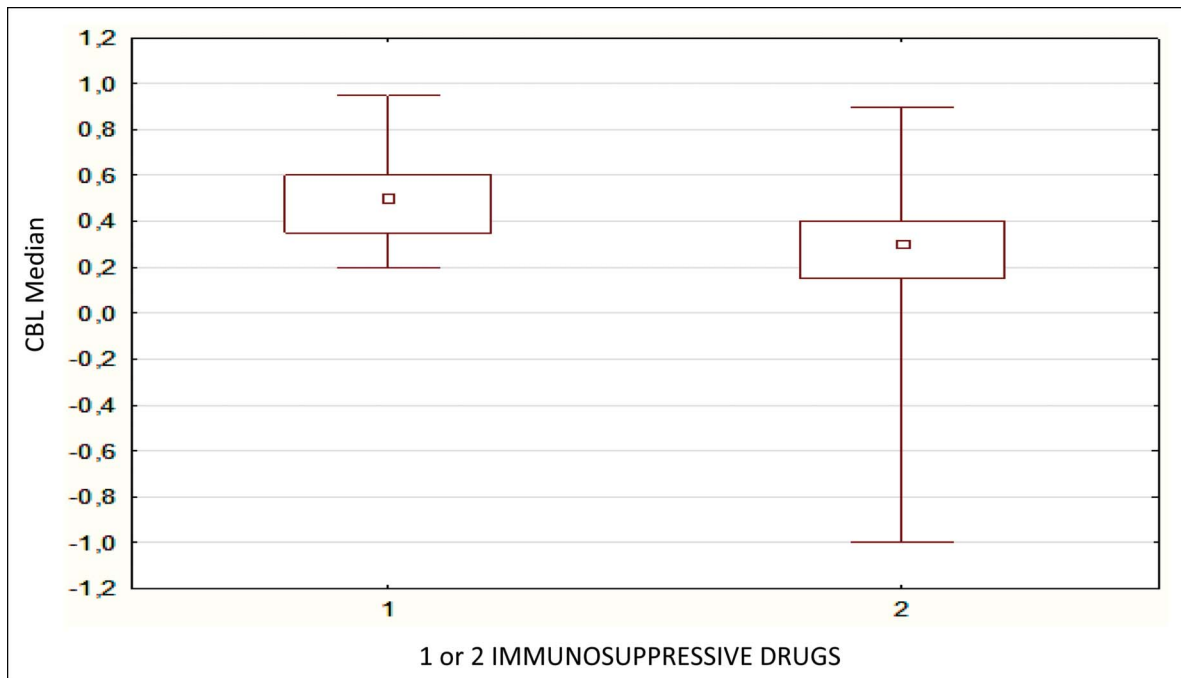


Fig. 5. Statistical analysis in the experimental group: a significant difference was observed in CBL between patients taking 1 or 2 immunosuppressive medications ($P = 0.042$). Results shown in a graphic form.

The observation period lasted at least 8 years. The results obtained in our study are a little different. Diversity of the outcomes (lower bone loss in this study) is most likely caused by another implantation technique (all implants placed subcrestally), a shorter follow-up period (minimum 24 months), and different immunosuppression regimes. Similar results were obtained by investigators Gultekin et al.³³ In their experimental group, where they applied comparable implants and surgical techniques, bone loss equaled 0.35 ± 0.13 mm after 15 months since implantation. Also, Annibali et al.³⁴ arrived at the result of the CBL median (MD) at the level of -0.55 mm, $[-0.86; -0.24]$, and in their experiment, they used implants of analogous construction as ours. In the study projects mentioned earlier,¹³⁻¹⁸ the largest group of patients

subject to immunosuppressive treatment regime took cyclosporin as the basic medication. It is a well-known fact that it is a medicine of the strongest negative impact on the process of bone healing around the implants.³⁵ Most patients included in our study have been administered tacrolimus. This confirms the hypothesis that more contemporary medications exert considerably lower influence on osseointegration and are less toxic to bone³⁶ and solid organs of the patient.³⁷ What is more, over the years the scale of “permissible bone loss” has been substantially reduced. What used to be considered as an ordinary process,^{30,31} nowadays is treated as a failure and happens more and more rarely.³⁸ Further follow-up of the patients should allow to confirm that the selected surgical technique and most of all appropriate immunosuppressive

therapy shall induce the reduction of CBL. The authors extended the originally planned follow-up period up to 5 years, with the ensuing checkups taking place after 3, 4, and 5 years accordingly. Based on the findings arrived at so far, one can claim that an increase in the bone loss surrounding implants is neither caused by immunosuppression in the form of single medication (be it tacrolimus, cyclosporin, sirolimus, or mycophenolic mofetil), nor caused by any additional application of steroids (Encorton and Metypred). Only in the case of combination therapy with 2 immunosuppressive medications (nonsteroids), a statistically noteworthy difference was observed ($P = 0.042$). However, even in this context, the bone loss was minor and insignificant for implant stability (Table 6).

The question which was of special interest to the investigators working in the present project, was the impact of taking glucocorticosteroids (GS) on the healing bone surrounding the implant inserted in patients with organ transplants. The effect of these medications on bone structures is commonly known and well documented,^{4,5,39,40} especially in the case of immunosuppressive therapy with the use of these substances

Table 3. Correlation Between CBL and Steroids

Variable	U Mann-Whitney Test (With Continuity Correction Against the Variable: Steroid)				P
	Rank-Sum Group 1	Rank-Sum Group 2	Valid N Group 1	Valid N Group 2	
CBL median	185.0000	115.0000	17	7	0.085633

Table 4. Assessment of Implant Stability on the Day of the Procedure—ISQ1 and After the Osseointegration Period—ISQ2

Class	Quantity Chart: ISQ1 Ranges			Class	Quantity Chart: ISQ2 Ranges		
	Quantity	Accumulated Quantity	Percentage		Quantity	Accumulated Quantity	Percentage
55–59	1	1	2.56410	55–59	4	4	10.52632
60–69	10	11	25.64103	60–69	16	20	42.10526
70–100	28	39	71.79487	70–100	18	38	47.36842

Table 5. Impact of Immunosuppressive Therapy on Secondary Stability of Implants 4 Months After Implantation (ISQ2)

Immunosuppression	ISQ2
1 medication	Median 70.5 (min 60–max 77)
2 medications	Median 70 (min 59–max 78.5)

applied after transplantations. GS influence not only bone metabolism but also to a large extent disturb the processes of soft-tissue regeneration. In this study, however, no negative impact of GS has been observed. No statistically significant disparities in the CBL were found between patients taking GS and patients not taking GS within immunosuppressive therapy. What is more, no difference was observed between either of these groups and the patients from the control group. OTPs take high dosages of GS for many years. Based on the findings of our investigation, one may assume that the administration of these medications does not significantly influence the process of implant osseointegration. The research done by other authors also provides confirmation of this fact.⁴¹ This observation is especially valuable in view of very common application of GS in numerous diseases, which gives a chance to safely implement implantoprosthesis treatment in these patients as well.

Measurements of bone loss allow to reliably assess any alterations taking place over a long period of time. They are, however, fraught by certain errors. These first of all results from the fact that the obtained results are subjective (even despite the application of the read-out method by 2 independent researchers and calculating the median). Thus, the authors decided to perform additional objective measurements, aiming at a comparison of the quality of the bone site and osseointegration process. The first method assumed the need to measure the torque necessary to insert the implant. This helped to evaluate the primary stability of the implant, while indirectly facilitating the characteristics of the bone site quality. The obtained results indicate no statistically significant differences in the torque value between the OTG and control group. This means that bone conditions were very good in all the patients included in the study, even despite the use of immunosuppressive treatment in the OTG. It gives another

confirmation of the assumption that there is no significant influence of this therapy on bone condition within the jaw and the mandible. The other method is the objective measurement of implant stabilization ISQ, which has a well-proven prognostic value.⁴² The researchers performed the measurement twice: on the day of implantation and after 4 months, which were adopted as a period indispensable for correct osseointegration. The obtained results indicate lack of significant impact of the applied immunosuppressive therapy on the secondary stabilization of implants. It does not matter whether a patient takes 1 immunosuppressive medication or 2, or whether he/she is treated with steroids. In all the cases, the results are higher than 55 ISQ. Almost identical results were obtained by researchers⁴³ in 2017, measuring bone loss and implant stabilization, what is more, based on measurements acquired only in a group of healthy patients.

One of the keys to successful treatment is the minimization of the risk of complications in that specific group of patients who take immunosuppressive medications. It is crucial to perform regular checkups and comply with appropriate hygienic requirements.⁴⁴ The basic issue is, however, a suitable antibiotic therapeutic regime, which has been applied to all the patients encompassed by our study. Despite the fact that it is not conclusively specified whether post-operative infections and implant failures can be reduced by the application of antibiotics and there are no adopted standards related to that issue,⁴⁵ the authors, similar to Ziebolz et al,³ recommend the use of these medications because of the increased infection risk in patients in the course of immunosuppression. Analogous conclusions that implant treatment is feasible in immunocompromised patients when proper precautions are taken were drawn by Vissink et al., 2018.⁴⁶

Table 6. Comparison of Results (Basic Measured Parameter—Bone Loss CBL) Obtained in Various Experiments

	CBL in the Experimental Group	CBL in the Control Group	Observation Time
Radzewski and Osmola	0.33 ± 0.95 mm	0.5 ± 1.8 mm	2 y
Fransson et al ³⁰	1.68 ± 1.3 mm		5 y
Gu and Yu ¹⁴	1.30 ± 1.3 mm		3 y
Montebugnoli et al ²⁶	0.28 ± 0.2 mm	0.42 ± 0.32 mm	3 mo
Annibali et al ³²	0.55 ± 0.86 mm		2 y
Gultekin et al ³¹	0.35 ± 0.13 mm		15 mo
Paredes et al ¹⁶	1.53 ± 0.6 mm	1.64 ± 1.3 mm	8 y

CONCLUSION

Immunosuppressive medications administered to the participants of our study—patients after organ transplants (kidney, pancreas, and liver)—do not have any impact on the osseointegration of dental implants. Implant stability and bone loss are not any different from those in healthy people. Steroids applied to OTPs have no influence on the effect of dental implant treatment, either at the bone level or soft tissues. Patients with organ transplants can safely and effectively undergo dental implant treatment. The condition is to adhere to appropriate procedures and postoperative checkups. The results arrived at in this study should become a significant contribution to further research of the group of patients submitted to immunosuppressive treatment, also for reasons other than transplantation.⁴⁷ The subsequent acquisition and confirmation of comparable results among those people as well shall give opportunity to improve life quality of a vast group of patients.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

APPROVAL

Ethics approval was obtained on October 13, 2013, from the Ethics Committee of the Poznan University of Medical Sciences (reference number 1234/2013).

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