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Does oral health contribute to post-transplant complications in kidney allograft recipients?

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Abstract

Objective. The significant number of complications in kidney graft recipients can not be easily explained. The paper assesses whether poor oral health increases the risk of acute rejections and hospitalizations in kidney allograft recipients. ***Materials and methods.*** Ninety-one kidney transplant recipients were divided into three sub-groups according to post-transplant time (< 1, 1–5 and > 5 years). Dental examination evaluated oral hygiene index (OHI-S) and Community Periodontal Index of Treatment Needs (CPITN), which were correlated with the occurrence of post-transplant complications. ***Results.*** Within the first year after transplantation the indicators of the increased risk of hospitalizations and acute rejection episodes was the OHI-S (hazard ratio 1.02 and 1.11, respectively), also CPITN score correlated with acute rejections ($R = 0.82$, $p < 0.01$). ***Conclusion.*** The neglect in oral health is associated with the increased risk of clinical complications within first year after kidney transplantation.

Key Words: *acute rejection, hospitalization, kidney transplantation, oral health indices*

Introduction

The overall care of transplant recipients and advances in immunosuppressive regimens have significantly improved both short- and long-term kidney allograft survival rates, but grafts continue to fail [1–3]. In the last decade, a significant decrease of graft loss due to acute rejection or chronic rejection was noted; however, no change in kidney transplant loss due to infection was observed, irrespective of considering long or short survival time (1.5–3.8% of overall causes) [1–4]. Elevated levels of markers of inflammation (e.g. C-reactive protein, interleukins, etc.) are associated with worse kidney allograft outcomes [5]. Even now, renal transplant recipients still remain at a higher risk of hospitalization incidences due to bacterial infection (including septicemia), which is associated with decreased survival of both the graft and the patients [6]. The process of patients' preparation to kidney transplantation, beside nephrological and urological specific procedures, incorporates the pre-transplant elimination of local infection in the oral cavity [7,8]. Once controlled, proper oral health status has to be monitored and verified once a year in yearly repeated routine follow-ups. The purpose of those visits is to guarantee the maintenance of a good general status of the patient, including oral health, to the moment of kidney transplantation and subsequent immunosuppressive treatment [9,10]. However, after transplantation, maintenance of proper oral health and hygiene may be neglected. Untreated dental caries and periodontal disease may become a source of infection, which may affect kidney graft function in both the short- and long-term [11,12], although to confirm this statement no hard proof has been established. Traditionally, immunologic factors and therapies have been considered in kidney transplant (kTx) outcomes and less attention has been paid to non-immunologic factors [3,13,14]. Neither untreated dental infection nor oral mucosa lesions can be underestimated and both may implicate several potential complications which can jeopardize the maintenance of renal function [15].

The aim of this study, therefore, was to determine whether any neglect in oral health may increase the risk of post-transplant complication.

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Materials and methods

We conducted the retrospective, cross-sectional study on 91 patients aged 22–71 years (male 59, female 32) who underwent kidney allograft transplantation from deceased donors within the last 10 years (1998–2008). All patients were treated in the Outpatient Clinic of Barlicki University Hospital No 1, Department of Kidney Transplantation, Medical University of Lodz. After informed consent had been obtained, patients' charts were evaluated and participants were asked in detail of their previous medical history (i.e. cause of end-stage renal failure, dialysis modality and dialysis vintage, number of kTx procedures, post-transplant time) during routine control visit in the out-patient clinic. The nephrological examination was accompanied by dental evaluation. On subsequent visits, the collected data was analyzed to find cases of acute graft rejections, deterioration of the graft function and hospitalizations (including exclusively infectious complications or deterioration of kidney transplant function but not concomitant disease exacerbation episodes). For statistical analysis, patients were retrospectively divided into three sub-groups according to post-transplant time, i.e. less than 1 year, 1–5 years and over 5 years. These three post-transplant intervals were successfully introduced by Matas et al. [1] in 2002 to identify the causes of graft loss and to determine potential intervention options. All data is shown in Table I.

The age profiles of the three sample groups were representative of the overall study population (43.5 years at $p > 0.05$) except <1 year after kTx, although the male–female ratio was only mirrored in the 1–5 years from kidney transplantation sub-group. The most frequent cause of end-stage renal disease was glomerulonephritis (47%) in all patients and it constituted over 60% of participants <1 year after kTx. The majority of participants prior to kidney allograft transplantation were treated with hemodialysis (87%). The mean dialysis vintage was shortest in the 1–5 years group—Table I.

Immunosuppressive medications

The immunosuppressive treatment comprised four protocols: cyclosporine A + azathioprine (CysA + AZA), 36 patients; cyclosporine A + mycofenolane mofetil (CysA + MMF), 25 patients; tacrolimus + azathioprine (TAC + AZA), six patients; and tacrolimus + mycofenolane mofetil (TAC + MMF), 24 patients. Only participants who continued therapy with one protocol were enrolled in this study. Immunosuppressive drug blood concentrations were assayed every visit as routine and adequate doses of calcineurine inhibitors were adjusted to maintain their reference values and achieve possible optimal graft time survival [16].

Clinical evaluation

The study protocol was approved by the Bio-Ethics Committee of Medical University of Lodz. We conducted our study in compliance with the principles of the Helsinki Declaration.

Dental examination was performed according to the WHO criteria for epidemiological studies by qualified dentist [17]. Teeth were examined visually and by dental probe inspection. To express caries intensity, the DMFT Index (Decayed, Missing and Filled Teeth) was calculated. Also, the Treatment Index (TI) was computed: the number of filled teeth to the number of carious teeth plus filled teeth. Oral hygiene was evaluated using the oral health index (OHI –S).

The gingival status was examined, the presence of gingival overgrowth was evaluated and scored according to the proportion of the labial surface of the tooth crown overlapped by gingival tissue: score 0 = normal gingivae, score 1 = overgrowth up to one-third of the labial surface, score 2 = overgrowth up to two-thirds and score 3 = covering more than two-thirds—according to criteria described by Kshirsagar et al. [8] and Nunn et al. [18]. To assess periodontium status and treatment needs, the CPITN index (Community Periodontal Index of Treatment Needs) was evaluated according to scores: 0 = healthy periodontium, 1 = gingival bleeding during probing, 2 = dental calculus, 3 = periodontal pockets (with interproximal attachment loss) 4–5.5 mm, 4 = periodontal pockets 6 mm depth.

Kidney allograft function was evaluated according to serum creatinine concentration (Cr) and urinary excretion of proteins, which was calculated as milligrams of proteinuria per 1 mg urinary creatinine—mg/mg Cr. All of those were measured using standard automated clinical chemistry analyzers on the day of clinical and dental evaluation. Then creatinine (CCI) and proteinuria changeability indices (PCI) (current value *minus* initial value) were computed. The higher index values indicate worse graft function prognosis.

Statistical analysis

The data was expressed as mean ± standard deviation. To compare the occurrence of potentially contributory variables in sub-groups the analysis of variance (Kruskal-Wallis one-way ANOVA) was used. The Cox proportional hazard ratio analyses were calculated. The effects of dental status on hospitalization and acute rejection risk were reported as hazard ratios and 95% confidence intervals (95% CI). The relations between variables were analyzed by calculating Spearman rank (R) correlation coefficients. Results of the statistical tests were considered significant at $p < 0.05$. Statistical analysis was performed using Statistica for Windows software (version 10.0).

Table I. Patients characteristic and results in all participants and in sub-groups divided according to time from transplant procedure.

Time from transplant procedure	All patients	< 1 year	1–5 years	> 5 years
Number of patients	91	27	32	32
Age, mean ± SD (years)	43.5 ± 12.0	40.1 ± 8.7[a,b]	42.7 ± 11.7	46.9 ± 13.7
Male (*n*)	59	18	25	16
BMI, mean ± SD	24.6 ± 3.9	24.1 ± 4.7[a,b]	25.1 ± 5.2	24.9 ± 4.4
Causes of ESRD (*n*)				
Diabetes	17	3	7	7
Glomerulonephritis	43	17	12	14
Polycystic kidney disease	4	2	1	1
Hypertension	3	2	1	0
Chronic pyelonephritis	9	1	3	5
Others	15	3	7	5
Hemodialysis (*n*)	79	25	26	28
Peritoneal dialysis (*n*)	12	2	6	4
Dialysis vintage ± SD (months)	18 ± 6	10 ± 4[a,b]	21 ± 8	17 ± 5
Number of transplant				
1	82	26	29	27
2 or more	9	1	3	5
HLA typing (pts) ± SD	16.52 ± 2.3	16.4 ± 2.13	16.5 ± 2.61	16.6 ± 2.15
Immunosuppressive medication				
Cyclosporine A	61	19	22	20
Tacrolimus	30	10	12	8
Azathioprine	42	13	14	15
Mycofenolane mofetil	49	15	17	17
Smoking (*n*)	9	3	4	2
Diabetes (*n*)	27	9	8	10
Dislipidaemia (*n*)	33	12	10	11
Uncontrolled hypertension (*n*)	4	1	1	2
CIs abnormalities (*n*/year)	78	25	25	28
CMV infections (*n*)	24	7	8	9
CMV disease (*n*)	3	3[a,b]	0	0
DT ± SD	1.0 ± 1.69	0.8 ± 1.5[a]	1.25 ± 1.6	1.0 ± 1.87
MT ± SD	10.4 ± 7.2	7.5 ± 4.4[a,b]	11.6 ± 8.7	10.7 ± 7.8
FT ± SD	3.5 ± 3.1	3.7 ± 3.3	3.5 ± 3.5	3.2 ± 2.7
DMFT ± SD	14.9 ± 7.0	12.1 ± 4.8	16.3 ± 7.4	14.4 ± 7.8
TI ± SD	0.69 ± 0.39	0.72 ± 0.38[a,b]	0.67 ± 0.35	0.66 ± 0.42
OHI-S ± SD	1.3 ± 0.5	1.5 ± 0.7[a,b]	1.37 ± 0.6	1.2 ± 0.5
CCI ± SD	1.7 ± 2.6	1.17 ± 0.17	1.2 ± 0.19	2.5 ± 4.2[b,c]
PCI ± SD	0.26 ± 0.32	0.3 ± 0.3	0.13 ± 0.17[a,c]	0.35 ± 0.4
Hospitalization ± SD (number per year)	0.94 ± 1.0	1.4 ± 1.2[a,b]	0.8 ± 0.7	0.5 ± 0.6
Acute rejection ± SD (number per year)	0.27 ± 0.45	0.4 ± 0.5[a,b]	0.2 ± 0.42	0.16 ± 0.31

ESRD, end stage renal disease; CIs abnormalities, calcineurin inhibitor serum abnormality episodes; CMV, cytomegalovirus; HLA, Human Leukocyte Antigen molecules; TI, treatment index; DMTF, decayed, missing and filled teeth; OHI-S, oral hygiene index; CCI, creatinine (mg/dl); PCI, proteinuria changeability indices (mg/mg urine creatinine).
Values are presented as mean.
Differences were considered significant for $p < 0.05$ (Kruskal-Wallis ANOVA).
[a]< 1 year vs 1–5 years.
[b]< 1 year vs > 5 years.
[c]1–5 years vs > 5 years.

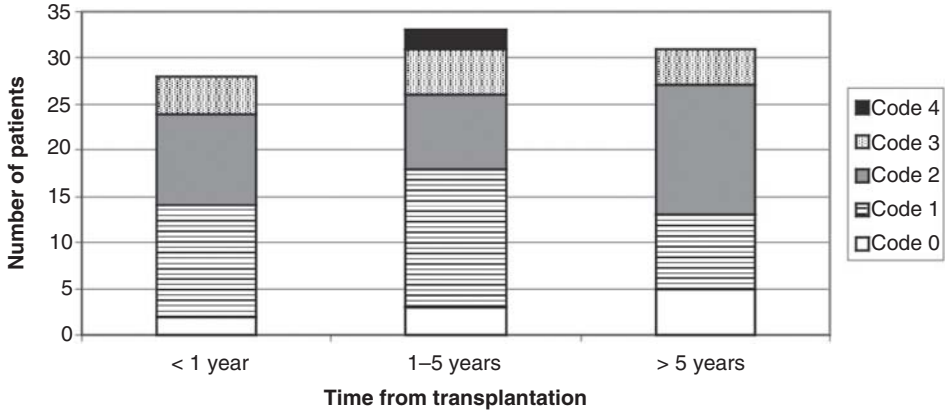

Figure 1. Distribution of CPITN codes in patients divided according to time from transplant procedure.

Results

Considering the factors which contribute to clinical complications, statistical analysis showed that immunosuppressive protocol types had no impact on hospitalization and acute rejection ratios. ANOVA analysis showed no differences between sub-groups in any of the variables, excluding lowered mean BMI, dialysis vintage; higher acute viral (cytomegalovirus) infection episodes, TI and OHI-S in the < 1 year after kidney transplantation sub-group or CCI and PCI in the >5 and 1–5 years from kTx sub-groups, respectively (Table I).

The <1 year post-transplant group demonstrated the lowest caries intensity, expressed by the DMFT index and isolated DT and MT components values, with the exception of FT value; the fewest number of filled teeth was noted in sub-group > 5 years after kTx. Statistically significant differences in the numbers of decayed (DT) and missed teeth (MT) between sub-groups <1 year and 1–5 years post-transplant were observed. A significantly lower number of missed teeth was noted in sub-group <1 year than in patients 1–5 and > 5 years post-transplant (both $p < 0.05$). No significant differences in the number of restored teeth were found, which indicates that the increase of caries experience was caused by a higher number of untreated caries lesions and by teeth extractions. The percentage of patients in whom no untreated carious lesions was found (TI = 1) was only 53.3% of all participants (fraction 0.63 in sub-group < 1 year, 0.38 in 1–5 years and 0.66 in >5 years post-transplant). The mean TI was the highest in patients who underwent kidney transplantation less than 1 year (TI = 0.72) and the lowest in sub-group > 5 year after kTx (TI = 0.66). The evaluation of oral hygiene showed that the OHI–S index was significantly higher in group <1 year after kTx than in the two other groups. The data is summarized in Table I.

The assessment of the CPITN index showed that only 11% of the examined subjects had no periodontal treatment needs (code 0). Code 1, which indicates a need for oral hygiene improvement, was noted in 39% of kidney transplant recipients and 35% needed professional scaling due to the presence of dental calculus deposits (code 2). Pathological pockets (code 3) were found in 12.8% of all participants. Code 4 were observed in two cases. Figure 1 shows the distribution of the CPITN codes in groups according to the time from kTx. ANOVA analysis of CPITN codes distribution showed no differences between sub-groups.

The drug-induced gingival enlargement was mainly noted in patients treated with cyclosporine A (72% polled) and only in three participants in whom tacrolimus was administered (overgrowth up to 1/3 of teeth labial surface). These three patients were treated with calcium channel blockers (amlodipine), which itself enhances the risk of gingival overgrowth [19]. The total number of patients suffering from hypertension and needing treatment with amlodypine, as a second anti-hypertensive drug, was eight (five in the group treated with cyclosporine). No correlations between immunosuppressive protocol and oral health indices were found, except gingival overgrowth. The gum overgrowth in patients treated with cyclosporine (immunosuppressive protocols CysA + AZA and CysA + MMF), irrespective of post-transplant time, was found (fraction 0.37, 0.43 and 0.68 for sub-groups < 1, 1–5 and > 5 years after kidney transplantation, respectively).

Further investigation indicates that the creatinine changeability index (CCI) increases with years after transplantation and finally reached 2.5 in the > 5 years from transplantation. In contrast, the proteinuria changeability index (PCI) rapidly decreased in sub-group 1–5 years post-transplant and differed statistically from the values for the other groups and the pooled patients. The number of hospitalizations per year decreased significantly with the number of years after kTx. Only in the early post-transplant period was a mean hospitalization rate higher than 1 per year observed (Table I).

Surprisingly, no significant increase in occurrence of factors typically regarded as contributory for kidney graft function evaluation and transplantation outcomes, i.e. creatinine and proteinuria changeability indices or no differences in Human Leukocyte Antigen molecules (HLA) typing score were observed.

The analysis of variances showed that both hospitalization and acute rejection ratios were highest in patients less than 1 year after kidney transplantation. The increased clinical complications ratio in the sub-group < 1 year after the transplantation implicated the need of further investigations.

Except for the < 1 year after transplantation group, no predictors of increased hazard ratio for hospitalization and acute rejection risk was established. The inadequate oral hygiene was regarded as an indicator which has aggravated hospitalization and acute rejection ratios within the first year after kidney transplantation. As well as DMFT, its components were not found as potentially associated with the occurrence of clinical complications. Similarly, creatinine and proteinuria changeability indices were unimportant in this regard. All statistical significances are described in detail in Table II. The immunological and non-immunological factors which may be considered as potential predictors of post-transplant complications were individually assessed; however, no contributory ones were identified (Table III). It is noteworthy that from variables pointed by ANOVA analysis as significantly different in the < 1 year after kTx group, none did correspond with the risk of hospitalization and acute rejection (Table III). The exception was the occurrence of cytomegalovirus (CMV) disease, i.e. CMV symptomatic infection, the only factor which impacted the hospitalization risk.

No correlations with oral health indices were noted except PCI and CPITN ($R = 0.74$, $p < 0.05$) in all participants, in sub-group < 1 year ($R = 0.7$, $p < 0.05$) and > 5 years after kTx ($R = 0.81$, $p < 0.05$). The CPITN index scores positively correlated also with the increased number of hospitalizations in all participants ($R = 0.47$, $p < 0.05$) and in sub-groups according to time from graft transplantation: <1 year ($R = 0.52$, $p < 0.05$), 1–5 years ($R = 0.55$, $p < 0.05$) and > 5 years ($R = 0.53$, $p < 0.05$). A relationship between the CPITN scores and acute rejection episodes was observed in patients less than 1 year after kTx ($R = 0.82$, $p < 0.01$).

Discussion

Kidney transplantation is decisively the most preferable method of kidney replacement therapy; it brings a greater rate of survival [20], a better quality-of-life [21] and a lower consumption of healthcare resources [15,22]. In the last decade, significant improvements of both short- and long-term post-transplant survival rates have been reported. Unfortunately still nearly one third of kidney transplant recipients suffer allograft loss within 5 years after transplantation [1]. In cadaveric donor graft recipients, except death with function (42%), main causes of graft loss are chronic rejection, thrombosis, non-compliance, acute rejection and infection (8%, 3.3%, 3.2%, 1.5% and 1.5%, respectively) [20,22]. In most of these, a chronic inflammatory state may be involved, inducing hypercoagulability and promoting an immunological response [15,23]. Chronic inflammation due to focus of infection significantly increases the risk of hospitalization and the hospitalization ratio of the renal transplant recipient due to severe infection can reach 41% [6]. However, many evaluations of the oral health status in patients with chronic kidney failure and in renal graft recipients have been widely described including oral microflora impact on patients or grafts survival rate [8,12,24,25], its influence on clinical complication risk rate in patients after kidney transplantation has been sporadically discussed but rarely reported [26–28].

In our study, the values of oral health indices describing oral hygiene and periodontal status seemed to be the predictors of both hospitalizations and acute rejection episodes in transplant recipients < 1 year post-transplantation. Surprisingly, changes in creatinine serum concentration or urinary protein excretion did not predict the incidences of post-transplant complications and remained only a reflection of a

Table II. Predictors of hospitalization and increased risk of acute rejection episodes in kidney transplant recipients—post-transplant time < 1 year (Cox multivariate regression).

	Hospitalization risk			Acute rejection episodes risk		
	Hazard ratio	95% Cl	*p*-value	Hazard ratio	95% Cl	*p*-value
CCI	1.53	1.42–1.55	NS	1.41	1.39–1.55	NS
PCI	1.76	1.69–1.81	NS	1.43	1.69–1.71	NS
DMFT	1.47	0.86–1.63	NS	1.44	1.51–1.84	NS
TI	1.34	1.18–1.49	NS	1.36	1.28–1.39	NS
OHI-S	1.02	0.98–1.12	< 0.01	1.11	0.98–1.15	< 0.01

CCI, creatinine (mg/dl); PCI, proteinuria changeability indices (mg/mg urine creatinine); DMTF, decayed, missing filled teeth; TI, treatment index; OHI-S, oral hygiene index.

Table III. Hospitalization and acute rejection risk potential predictors and they hazard ratio—post-transplant time < 1 year (Cox multivariate regression).

		Hospitalization risk			Acute rejection risk		
	Individuals (n = 27)	Hazard ratio	95% Cl	p-value	Hazard ratio	95% Cl	p-value
Age, mean ± SD (years)	40.1 ± 8.7	1.09	1.03–1.55	NS	1.07	1.05–1.25	NS
Male (n)	18	1.11	1.09–1.81	NS	1.16	1.09–1.71	NS
BMI, mean ± SD	24.1 ± 4.7	1.16	1.13–1.28	NS	1.22	1.18–1.29	NS
Smoking (n)	3	0.88	0.78–1.12	NS	0.92	0.83–1.22	NS
Diabetes (n)	9	1.27	1.23–1.55	NS	1.17	1.11–1.55	NS
Dislipidaemia (n)	12	1.16	1.09–1.81	NS	1.21	1.07–1.61	NS
Dialysis vintage (months)	10 ± 4	1.14	1.09–1.28	NS	1.19	1.07–1.38	NS
CMV disease (n)	3	1.09	0.98–1.11	0.0012	1.08	0.98–1.26	0.07

CMV, cytomegalovirus.

kidney allograft dysfunction. These suggest that, in the early period after kTx, any chronic inflammation and focus of infection may aggravate the risk of clinical complications. Within the first year after kTX patients are treated with the higher doses of immunosuppressive drugs to prevent host vs graft disease, which enhances infection risk. In subsequent periods the balance of immune reactivity including cellular and humoral response sets down, therefore, the decline of immunosuppressive regiments is possible and patients are less prone to any infection. Although the maintenance of graft function is the aim of the first year after allograft transplantation and follow-ups in the nephrology outpatient clinic are most frequent during this time, the pre-transplant good oral health status which has been achieved prior to the transplantation may be discontinued. Some authors suggests that mandatory pre-transplant sanation of the oral cavity, may be not meticulous [26,27] but, according to the principles of qualification to transplantation [10] this presumption seems not to be relevant and rather neglected oral hygiene (the highest OHI-S value was noted in the <1 year post-transplantation group) results in rapid worsening of oral health.

Poor oral hygiene increases cyclosporine-induced gingival overgrowth and also can lessen plaque-related gingival and periodontal diseases that are potential sources of oral infections [12]. A bacterial flora of anaerobes and microareophilia in gingival pockets can present a serious systemic threat. According to the literature, periodontitis strongly correlates with cardiovascular risk mortality in hemodialysis patients [8]. Additionally, a case of sub-hepatic abscess following bacteremia due to porphyromonas gingivalis causing periodontal disease has been reported in a renal allograft recipient [29]. Also our results highlight the correlation between periodontium status and clinical complications such as acute kidney graft rejections. In our study, carious lesions were detected in 47% of the graft recipients, an increasing number of decayed teeth were observed within the years after transplantation, as well as no significant differences in the number of restored teeth and a low Treatment Index value. It suggests the lack of dental attendance among patients after kidney transplantation, which is cause for concern as untreated caries lead to pulp complications and odontogenic infection. Greenberg and Cohen [11] reported that dental infections in kTx patients potentially contribute to morbidity and lead to transplant rejections, which was also reported by other authors [8,12]. Also Wilson et al. [30] described severe systemic spread of odontogenic infections in renal transplant recipients. According to the principles, the pre-transplant oral health status should be monitored and controlled to the moment of transplantation procedure [10]. Although receiving a kidney transplant is pivotal for every patient with chronic kidney failure (CKF) and leads to an enormous change in life habits, the patient's conviction of being cured from CKF may adversely affect the patient's adherence to the treatment, no matter how pre-transplant education of general and oral health was emphasized [31]. Beside the aggravation of inflammatory status, poor oral hygiene points to general health status worsening and possibly non-compliant patients [31].

Nevertheless, in our study, over 57% of participants were characterized by inadequate oral hygiene (OHI-S >1) and no signs of non-adherence were noticed (irregularity of visits in nephrology outpatient clinic or fluctuations of immunosuppressive drug serum concentrations), which suggests that neglect of oral health might result from a lack of knowledge of its importance and its influence on general health. The percentage of non-compliance patients was similar to results obtained by Laederach-Hofmann and Bunzel [31].

It is noteworthy that HLA typing score and episodes of abnormal calcineurine inhibitor serum concentration traditionally perceived as kidney transplant

predictors were not contributory factors in statistical analysis of the risk of complications. The results of ANOVA analysis pointed to oral health indices being significant variables which are worthy to be evaluated in the sub-group of patients <1 year after kTx, i.e. in the period when the immunosuppressive treatment is the strongest and infectious complications the most probable. Although our hypothesis, due to limitations, does not necessarily suggest the presence of causality (oral health may be considered rather as an indicator not a risk factor of clinical complications), the indicated association may have several implications in the population of kidney transplant recipients. The question is whether anything further might be done to improve post-transplant outcome and to reduce the influence of non-immunological factors on graft loss ratio and whether dental evaluation and treatment should be included. As an initial step, renal physicians should put special attention on educating post-transplant patients of the importance of good oral health, because it lowers the risk of oral infection and, thus, its systemic spread [32]. Also, the inclusion of a proper preventive and treatment dental plan within the interdisciplinary post-transplant care scheme may diminish the risk of clinical complications in kidney graft recipients.

This evaluation shows the need of further investigations, along with an interventional study to determine whether the results of the paucity of studies reporting the influence of oral health on graft survival and co-morbidities in renal post-transplant patients is causal. Furthermore, additional means of improving kTx outcomes should be investigated, including good oral health maintenance.

Conclusions

Our results suggest that neglect in oral health may be associated with post-transplant complications in the early period. A high oral hygiene index was regarded as an indicator of increased risk of hospitalization and acute rejection ratios within the first year after kidney transplantation. Additionally, periodontium status was recognized as, unrelated to time from the transplant procedure, a contributory factor which may conduct to the occurrence of clinical complications.

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