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Gingival enlargement in relation to periodontal parameters

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Gingival Enlargement

In Relation To Periodontal Parameters

by

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THESIS

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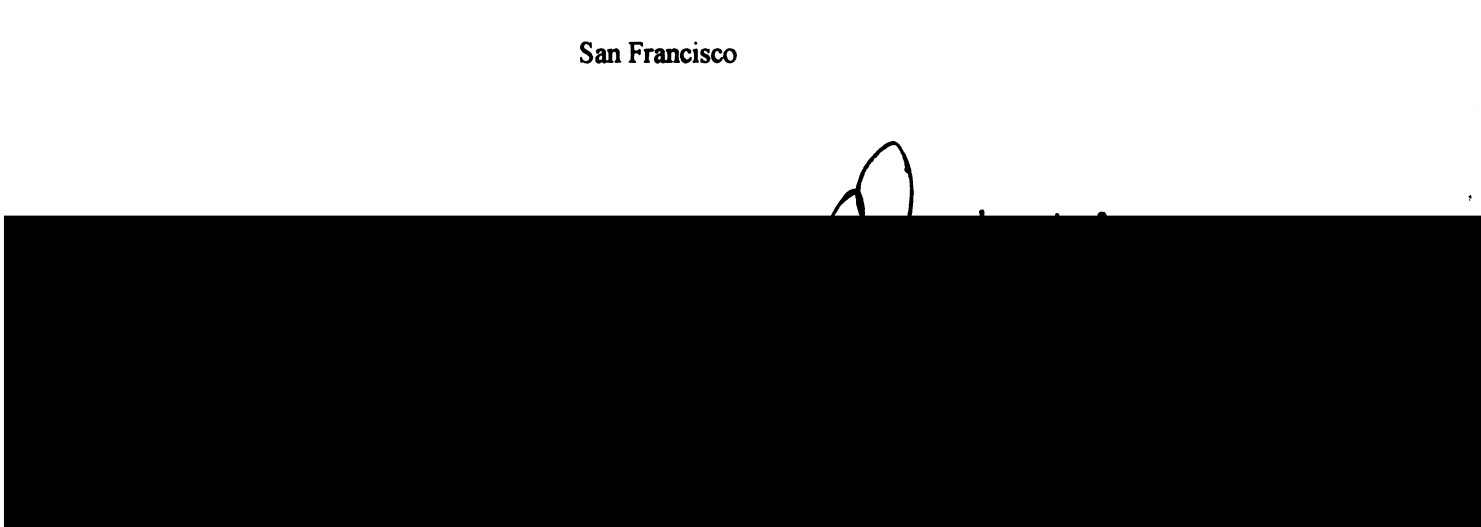

Dedication

In loving memory of my grandfather, Ulisse M. Cortopassi, who left Italy in search of a better life for his family in America and served as a source of inspiration throughout my education.

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INTRODUCTION

The relationship between systemic disease and periodontal disease has become an important issue in the dental and medical community within recent years. As these relationships become more defined and accepted, it will become important for both dental and medical professionals to consider this systemic-periodontal connection in both treatment planning and therapy. The relationship between systemic disease and periodontal disease is evident in renal transplant patients on anti-rejection therapy as specific anti-rejection drugs are known to cause gingival enlargement, which is often associated with periodontal disease. Knowledge about periodontal complications in transplant patients will lead to improved diagnosis and therapeutic options for the dental practitioner. The objectives of this dissertation are to 1) characterize a population of renal transplant recipients (RTRs) with respect to clinical periodontal parameters, and 2) explore these parameters in relation to the gingival enlargement (GE) that may occur as a result of specific anti-rejection drugs. A comprehensive literature review on many aspects surrounding GE and the drugs that may cause it is also included in this dissertation.

BACKGROUND & SIGNIFICANCE

The first successful renal transplant was performed in 1954 at the Peter Bent Brigham Hospital in Boston, Massachusetts.[1] At that same time, Peter Medawar, of Great Britain had shown that rejection of foreign tissue, which accounted for the high failure rate of renal transplants, was due to the host immune response.[2] Medawar's finding led to a standard of care that dictated that a renal transplant should only be considered when it

was certain that the patient would die without the transplant. The renal transplant in 1954 further confirmed Medawar's findings because the recipient and donor were identical twin brothers. Their identical genetic makeup eliminated any problem or concern with host rejection. In the fifty years since the first renal transplant, the number of renal transplants has continued to increase each year and it is now one of the most common organ transplant surgeries performed. As renal transplants become more common, dental professionals must be prepared to treat these patients and physicians must be aware of the possible oral implications of their therapy.

Initial attempts to suppress the recipient's immune response to allow for survival of transplants involved intense radiation therapy. Although, this therapy was successful in suppressing the immune response, it often proved to be fatal to the patient. In 1959, azathioprine (Imuran®), a purine synthesis inhibitor used in the treatment of leukemia, was shown to be effective in preventing post-transplant rejection. Between the years of 1954 and 1973, approximately 10,000 renal transplants were performed with greater success as a result of this new immunosuppressant.[1] The breakthrough in renal transplantation, however, came in the 1980s with the introduction of a new generation immunosuppressant, cyclosporin.[3] In 1986, nearly 9,000 kidney transplants were performed in the United States, with an 85% survival rate for the first year.[1]

Cyclosporin is a weak antimicrobial agent, but a good immunosuppressant that acts on T lymphocytes.[4,5] This drug has successfully been used alone and in combination with other medications for renal, hepatic, pancreatic, bone marrow, and cardiac transplants to control tissue rejection as well as several autoimmune diseases.[6] Cyclosporin works by interfering with T cell activation of B lymphocytes via selective

inhibition of T helper cells.[7,8] This apparent host modulation activity prevents the recipient's immune response from attacking and destroying the transplanted organ.

Although cyclosporin use has resulted in a significant increase in the success rate of renal transplants, the drug is not without side effects. Common side effects include nephrotoxicity, hypertension, hepatotoxicity, neurotoxicity, lingual fungiform papillae hypertrophy, and gingival enlargement.[6] Gingival enlargement associated with this drug tends to manifest within three months following the commencement of the drug therapy in 20 to 80% of patients taking this medication.[9] The effects of the medication, including gingival enlargement, may be enhanced as a result of co-treatment of other medications, including anti-hypertensive or anti-seizure drugs.[10] Drug-influenced gingival enlargement is associated with anticonvulsants, calcium-channel blockers, and the immunosuppressant cyclosporin. The combination of cyclosporin with calcium-channel blockers has been associated with increased prevalence of gingival enlargement as compared to mono-therapy.[11] Patients on nifedipine, a calcium-channel blocker, and cyclosporin following cardiac transplants were shown to have significantly higher gingival enlargement scores and periodontal probing depths when compared to transplant patients who were only on cyclosporin.[12]

Although there are new generation immunosuppressants that have fewer side effects, including fewer oral manifestations, cyclosporin is still given to renal transplant patients.[13,14] Patients who respond well to this medication, meaning that graft rejection is prevented, are maintained on cyclosporin, even in the presence of gingival enlargement. From a periodontal perspective, it is important to ask whether or not there is an association between clinical markers for periodontal disease, including probing depth,

attachment loss, plaque, calculus, and bleeding on probing, and the incidence and severity of gingival enlargement. An evaluation of this association may aid in the development of an objective method of assessing gingival enlargement based on periodontal measurements that are made during routine dental examinations. Periodontal measurements may be used to estimate the degree and extent of gingival enlargement among patients with gingival enlargement. An association between these factors may also allow for the identification of patients who are at a higher risk of developing gingival enlargement. This information may assist in developing protocols for pre- and post-surgical oral evaluations and also conditions necessary for successful periodontal therapy of gingival enlargement. Patients identified as being at higher a risk for developing gingival enlargement would be given additional instruction in oral hygiene and may also be seen by their dentist on a more frequent basis to monitor their gingival health.

The term gingival enlargement is used to classify an overall increase in the size of the gingiva that may be influenced by drug therapy.[15] The essential feature in all drug-influenced gingival enlargements is an increase in the amount of the connective tissue matrix.[16] The etiology of drug-influenced gingival enlargement, however, is not entirely understood. It is believed that there are two components to gingival enlargement, a fibrotic portion caused by the medication, and an inflammatory portion caused by the accumulation of bacterial plaque.[17] The existence of gingival enlargement poses a plaque control problem due to impaired access to the tooth surface and increased areas of plaque retention. It may also affect mastication, tooth eruption, speech, and cause esthetic concerns.

Although gingival enlargement is the current term of choice used to describe the disease, it has been given several other names throughout the literature. Previous terms have included gingival hyperplasia, gingival hypertrophy, gingival fibromatosis, and gingival overgrowth. Gingival hyperplasia was used to describe a fibrotic enlargement that resulted from of an increased number of cells within the tissue while gingival hypertrophy was the result of an increase in cell size, not number. The different terms were developed based on proposed etiologies of the gingival enlargement. For example, gingival hyperplasia was used to describe enlargement that was associated with non-inflammatory factors such as drug therapy. Therefore, the removal of etiologic bacterial factors from the tooth surface would not be expected to result in a significant improvement of gingival hyperplasia, but changing the causative medication would. Gingival enlargement has also been associated with systemic conditions including pregnancy, puberty, leukemia, and granulomatous diseases.

Gingival enlargement accentuates the depth of the gingival sulcus and produces areas that enhance plaque retention and accumulation. Plaque accumulation may result in inflammation that can lead to further enlargement and more plaque accumulation. Gingival enlargement does not affect all areas of the mouth with equal frequencies, but rather certain areas seem to be more susceptible. The buccal and labial surfaces of the canines and incisors seem to be more susceptible versus the lingual surfaces and the posterior teeth.[18] Typically, gingival enlargement begins in the interproximal gingival tissue and may continue to enlarge to converge with the adjacent papilla to appear to cover the entire tooth.[19] In severe cases, the enlarged papilla or papillae may cover the entire clinical crown. Gingival enlargement typically manifests within three months of

taking cyclosporin, however, as the duration and dosage of cyclosporin use increases, so does the incidence of gingival enlargement.[9,20,21] The progression of enlargement is usually slow and painless, however, it may be complicated by acute infection or trauma.

There is a lot variation that is seen among reports on the extent and severity of gingival enlargement. The differences are likely due to the method of assessment, the nature of the disease, the combination of the medications, and the age of the patient. [8] Currently, there is no "gold standard" for measuring gingival enlargement; therefore, it becomes difficult to compare the results of different studies. Photographs, casts, and various clinical measurements have been used and although each method has benefits, none effectively and objectively quantify gingival enlargement. The most recognized index at this time may be the Seymour Index of gingival enlargement. This index uses measurements taken from study casts to quantify the amount of gingival enlargement present. Although this method is often used, it may not be practical to use in larger studies because of the time and expense involved in obtaining casts of patients. If periodontal parameters that are routinely recorded during examinations can be correlated to gingival enlargement, it may become possible to use these parameters as surrogates for the risk of developing gingival enlargement.

Gingival enlargement associated with cyclosporin use was first described in periodontal patients in 1983; however, gingival enlargement was noted in the initial cyclosporin clinical trials and was reported in the medical literature in 1980. [22,23] Although it has been many years since the initial description, the exact mechanism of the initiation of gingival enlargement in patients on cyclosporin is not well understood, but several modifying factors have been investigated. The initiation and progression of

gingival enlargement is likely influenced by the presence of pathogenic oral microorganisms that exist within plaque on the tooth surface. Gingival enlargement has been shown to increase in the presence of plaque and decrease and occasionally resolve in the presence of improved oral hygiene.[9,24,25] Although some studies have shown that oral hygiene can control gingival enlargement, others have shown that plaque control and the existence of local factors alone cannot explain the presence of gingival enlargement.[26-28]

Approximately 30% of individuals on cyclosporin experience gingival enlargement that is severe enough to require some type of periodontal therapy.[9] Changing the anti-rejection medication to an alternate medication has been shown to reduce gingival enlargement in some patients.[29] A new generation anti-rejection medication, tacrolimus hydrate (Prograf®), is not associated with adverse effects on the gingival tissues, and may prove to be a good alternative to cyclosporin therapy.[14] In addition, tacrolimus has also been shown to reduce acute rejection episodes when compared with cyclosporin therapy.[30] Non-surgical periodontal therapy including coronal polishing, scaling, and scaling and root planing has been shown to be effective in reducing cyclosporin-influenced gingival enlargement.[29] The reduction in gingival enlargement seen with non-surgical therapy is likely due to a resolution of the inflammatory component of the gingival enlargement. Systemic antibiotics such as metronidazole and azithromycin have been used in conjunction with non-surgical therapy. Although these drugs do not reverse gingival enlargement, their use has been shown to reduce the inflammation that results in the selection or activation of a subpopulation of fibroblasts that react in the presence of cyclosporin, leading to gingival enlargement.[31]

Although non-surgical therapy may control gingival enlargement, residual periodontal pockets may result in the need for surgery to establish a healthy and maintainable periodontium. Surgical intervention is required in about half of patients treated for gingival enlargement, and although surgical therapy is more aggressive, recurrence is still common.[32] Surgical therapy may include either gingivectomy or periodontal flap procedures. A gingivectomy, performed via an external bevel incision, is faster and allows for removal of the excess tissue, however, it may result in the loss of keratinized tissue and the creation of mucogingival defect.[17] The goal of this therapy is to restore the physical contour that is seen in healthy gingival tissue. Periodontal flap procedures utilizing the internal bevel incision heal by primary intention and can preserve the existing keratinized tissue.[17] This procedure also allows for subgingival debridement and osseous recontouring that may be indicated for patients with loss of periodontal attachment and bone. Shallower probing depths have also been noted following periodontal flap surgery when compared to gingivectomy.[33]

After the initial removal of excess tissue in patients with gingival enlargement, a comprehensive maintenance program is critical. Chlorhexidine rinses have been shown to be effective in maintenance programs following therapy.[34] Frequent periodontal maintenance recalls are necessary to maintain minimal plaque and bacteria levels and to minimize recurrence of the gingival enlargement. Recurrence is common and severe gingival enlargement has been noted in one third of treated patients within an 18-month period.[35] It is therefore, important to identify risk factors to minimize and control recurrence in patients with gingival enlargement. The first step in identifying risk factors

for gingival enlargement is to evaluate possible relationships between common periodontal measurements and gingival enlargement.

OBJECTIVE

The objectives of this study were to characterize a population of adult RTR with respect to clinical parameters of periodontal heath, and to explore the degree of gingival enlargement in relation to these parameters, specifically: 1) to explore a possible association between clinical assessments of gingival inflammation and a visual index of gingival enlargement; 2) to explore a possible association between probing depth and clinical attachment loss and a visual index of gingival enlargement. The hypothesis of this study is that the clinical assessment of inflammation and clinical measurements of probing depth and clinical attachment levels are strong predictors of the presence and extent of gingival enlargement within a population of renal transplant patients on anti-rejection therapy.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted on renal transplant patients on anti-rejection drug therapy who were being treated at the University of California, San Francisco Renal Transplant Center. Some of the medications included in the anti-rejection therapy have been previously associated with gingival enlargement. The U.C.S.F. Committee on Human Research approved the study protocol.

Study Population

Subjects were recruited from the Kidney Transplant Unit (KTU) at the University of California, San Francisco Medical Center. All patients present in the waiting room of the KTU during visits by clinical research assistants, who identified themselves as renal transplant recipients, and who were at least 6 months post-transplant, were invited to have an oral evaluation at the Oral Medicine Clinic located at the University of California, San Francisco School of Dentistry. Patients were recruited by clinical research assistants (who obtained written informed consent) and were scheduled for oral evaluations that were completed at a later date by Dr. Caroline Shiboski (Principal Investigator), director of the Oral Medicine Clinic, and/or Drs. Kevin Consani and Katja Greenberg, periodontal residents from the Division of Periodontology at the University of California, San Francisco School of Dentistry. Clinical research assistants extended invitations for evaluations during multiple visits to the KTU each week. Two half-day 3-hour periods were available each week for patients to schedule their evaluations.

Inclusion criteria

1. Present for oral evaluation at the Oral Medicine Clinic
2. Signed informed consent form
3. Renal transplant at least 6 months prior to our initial evaluation
4. Able and willing to take required antibiotic prophylaxis as recommended by attending physician at RTC
5. On immunosuppressive anti-rejection therapy at the time of evaluation

6. Absence of medical conditions/infections that prevent the completion of a periodontal examination
7. ≥18 years of age

Exclusion criteria

1. Patients unable to attend visits at the Oral Medicine Clinic
2. Unwilling or unable to give consent for examination
3. Renal transplant within 6 months of presentation of examination
4. Unable or unwilling to take recommended antibiotic prophylaxis
5. <18 years of age

Standardized Questionnaire

A standardized questionnaire was administered at time of enrollment to collect information about socio-demographic characteristics, health history, smoking and alcohol use, oral health history, and information regarding utilization of dental care services.

Oral Evaluation

Premedication

Prior to any oral evaluation, each patient was given an antibiotic prophylaxis at the request of the attending physicians at the U.C.S.F. Renal Transplant Center. Patients with no history of drug allergies were given 2 g of amoxicillin 1 hour before their

examination. Patients with an allergy to penicillin were given 600 mg of clindamycin 1 hour before their periodontal examination.

Oral Mucosal Lesions

Dr. Caroline Shiboski conducted a visual soft tissue evaluation of the oral tissues and the color, character, location, and clinical diagnosis of any intraoral lesions were recorded. Examinations were conducted in a dental clinic using an overhead light, a dental mirror, and 2x2 gauze. Clinical photographs were also taken using a 35 mm camera and a micro-zoom lens with ring flash.

Periodontal Evaluation

A complete periodontal examination was performed on all eligible patients who presented to the Oral Medicine Clinic. Drs. Shiboski, Consani, or Greenberg conducted the clinical examinations and the clinical research assistants recorded the findings. If the clinical research assistants were not available, clinical information was dictated into a tape recorder by the examiner and transcribed at a later time by the assistant. Examinations were conducted in a clinical suite utilizing a dental chair and overhead light. Clinical attachment levels of all remaining teeth, excluding third molars was determined, using a University of North Carolina periodontal probe with one-millimeter

incremental markings. Information collected at the initial exam included probing depths (PD: gingival margin to base of the probeable pocket) and positive or negative recession (R: cementoenamel Junction (CEJ) to gingival margin, negative if gingival margin was covering the CEJ and positive if the CEJ was exposed above the gingival margin). These measurements were used to calculate attachment loss (CEJ to the base of the probeable pocket). All examiners were calibrated to a "gold standard", Dr. Robert Wirthlin, and achieved a minimum of 98% agreement on all measurements within 1 millimeter taken with the University of North Carolina Probe. Bleeding on probing (yes/no), plaque (Löe and Silness)[36], and calculus (Ramfjord)[37] were also evaluated. Gingival enlargement was evaluated using a visual index developed by Aas [28]. All measurements and indices, with the exception of gingival enlargement, were recorded at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual). The measurements for gingival enlargement were recorded for each sextant (maxillary and mandibular posterior right, anterior, posterior left). The following clinical indices were recorded:

Plaque Index PlI(Löe and Silness)[36]

- PlO no plaque at the gingival area
- Pl1 no visible plaque, but noted upon sweeping tooth with probe
- Pl2 gingival third of tooth covered with a thin visible deposit of plaque
- Pl3 abundance of plaque at the gingival third of the tooth and covering the Gingival margin

Bleeding on Probing

BOP= 0 no visible bleeding upon probing

BOP= 1 visible bleeding upon probing

Calculus Index (Ramfjord)[37]

C=0 absence of calculus

C=1 supragingival calculus that extends 1mm or less below the gingival margin

C=2 moderate supra- or subgingival calculus

C=3 abundance of supra- and subgingival calculus

Gingival Enlargement Index (Aas)[28]

GE=0 no gingival enlargement

GE=1 mild gingival enlargement covering <1/3 of the clinical crown

GE=2 moderate gingival enlargement covering ½ of the clinical crown

GE=3 severe gingival enlargement covering 2/3 of the clinical crown

GE=4 severe gingival enlargement covering the entire clinical crown

Each patient was given a written summary of findings, and recommended treatment to give to their general dentist and to their physician at the KTU. If the patients did not

have a general dentist, a referral list, including local dentists and the schools of dentistry located at U.C.S.F. and the University of the Pacific, was given to the patient.

When a patient was found to need periodontal treatment and did not have an existing source of care, appropriate periodontal therapy was performed as follows:

1. Oral hygiene instruction, tailored to the needs of the patient, given at the clinical evaluation
2. Scaling and root planing as needed, completed in the post-graduate periodontal clinic at U.C.S.F. following the clinical evaluation
3. One-month re-evaluation to assess the gingival response to initial therapy and home care, completed in the post-graduate periodontal clinic at U.C.S.F. following the scaling and root planing
4. Surgery, including gingivectomy, flap osseous surgery, and extractions, completed in the post-graduate periodontal clinic at U.C.S.F. following the one month re-evaluation

Statistical Analysis

Summary statistics of sample characteristics and periodontal parameters

Proportions were used to describe the sample with respect to socio-demographic variables (categorized age, gender, and race/ethnicity). To summarize periodontal clinical parameters, we computed the per-participant percent of sites with each parameter defined as follows:

*Visible plaque (or % of sites with plaque index > 1)

*Bleeding on probing (or % of sites with BOP=1)

*PD $\geq$ 4 mm (or % of sites with PD $\geq$ 4) and PD $\geq$ 5 mm (or % sites with PD $\geq$ 5)

*CAL $\geq$ 3 mm (or % of sites with CAL $\geq$ 3) and CAL $\geq$ 4 mm (or % sites with CAL $\geq$ 4)

*Recession ≥ -3 mm (or % of sites with 3 mm or more of anatomical crown covered)
*Recession ≥ -4 mm (or % of sites with 4 mm or more of anatomical crown covered)

We examined the distributions of these clinical parameters by computing both the mean and median, then by categorizing them using a grouping that seemed appropriate to best describe the distribution.

Analyses exploring GE by clinical periodontal parameters

Bivariate analyses

The prevalence of GE was defined as the ratio of participants having any severity and extent of GE over the total number of dentate participants who received an oral examination (one edentulous subject was excluded from the analysis). The distribution of the various grades of GE was also explored. However, due to the small proportion of participants with higher grades of GE, we used a dichotomous variable to explore GE in relation to medication status. We used two approaches to explore potential associations between GE and periodontal parameters. We first used a non-parametric analysis (Mann-Whitney test) to compare the per-participant percent of affected sites (for each parameter) in the group with GE and the group without. We then used contingency tables and chi-square or Fisher's exact tests to explore the association between GE and the categorized clinical periodontal parameters.

Multivariate analysis

Logistic regression models were fit to explore the association between each clinical periodontal parameter and GE while controlling for the effect of calcium-channel blockers. Indicator variables were created for each clinical periodontal parameter as follows:

Plaque index: A reference group included patients that had 10% or fewer sites with visible plaque. The categories fitted in the model and compared to the reference group were > 10% and up to 40% sites with visible plaque, and > 40% with visible plaque.

BOP: A reference group included patients that had 10% or fewer sites with BOP. The categories fitted in the model and compared to the reference group were > 10% and up to 30% sites with BOP, and > 30% with BOP.

PD ≥ 4 mm: A reference group included patients that had 10% or fewer sites with PD ≥ 4 mm. The categories fitted in the model and compared to the reference group were > 10% and up to 30% sites with PD ≥ 4 mm, and > 30% with PD ≥ 4 mm.

Recession ≥ -3 mm: A reference group included patients that had 10% or fewer sites with Recession ≥ -3 mm. The categories fitted in the model and compared to the reference group were > 10% and up to 30% sites with Recession ≥ -3 mm, and > 30% with Recession ≥ -3 mm.

Recession ≥ -4 mm: A reference group included patients that had 10% or fewer sites with Recession ≥ -4 mm. The categories fitted in the model and compared to the reference group were > 10% and up to 30% sites with Recession ≥ -4 mm, and > 30% with Recession ≥ -4 mm.

We fit individual models for each clinical periodontal parameter, because there was too much colinearity between parameters to allow inclusion of all parameters in the same model.

The measures of association yielded by the logistic model were adjusted odds ratios (adjOR) with 95% confidence intervals (95%CI).

Results

Demographic and clinical sample characteristics

Data was collected on a total of 122 patients who were recruited from the renal transplant center at U.C.S.F. To maximize patient participation, oral evaluations were usually scheduled as to follow evaluations in the renal transplant clinic. Evaluations were done at one visit and took approximately one hour.

The patient group consisted of essentially equal numbers of males and females. The majority of patients evaluated were Caucasian, followed by Hispanics, Asians, and African Americans. Half of the patients were of 46 years of age or older and 75% of subjects were over the age of 36 years or older (Table 1). Table 2 summarizes the number of patients on immunosuppressant medications with and without the use of calcium-channel blockers. 40% of the patients were taking cyclosporin, 30% were on calcium-channel blockers, and 17% were on a combination of the two medications.

Each patient who was given a periodontal examination was evaluated for plaque, calculus, bleeding on probing, probing depth, and attachment loss. The extent of the evaluated parameters was reported in terms of per participant percent sites affected, as described in the Methods. An examination of summary statistics (mean and median) for the various periodontal parameters revealed that most of these variables did not follow a normal distribution (the mean differed substantially from the median due to either the presence of outliers in the data or because of a skewed distribution). As revealed by the median values in Table 3, half of the study sample had nearly 25% sites (approximately 7 teeth) which had visible plaque and CAL > 3 mm, while BOP was present on 10% or fewer sites and PD > 4 was found on 6% or fewer sites.

Table 1. Demographic characteristics of a sample of adult RTRs from the UCSF KTU

	SAMPLE NUMBER	PERCENT
RACE/ETHNICITY		
CAUCASIAN	43	35
ASAIN	25	21
HISPANIC	32	18
AFRICAN AMERICAN	22	26
TOTAL	122	100
AGE (YEARS)		
18-25	4	3
26-35	22	18
36-45	31	25
46-55	31	25
56+	34	28
GENDER		
MALE	64	52
FEMALE	58	48

Table 2. Summary of medications taken by the sample of RTRs

Medication	N
Cyclosporin*	49
Tacrolimus*	61
Neither**	9
Ca Channel Blocker	37
Cyclosporin + Ca Channel Blocker	20
Tacrolimus + Ca Channel Blocker	16
Ca Channel Blocker only	1

* These medications were taken in combination with prednisone (5 to 7.5 mg/d) and sometimes microphenolate mofetil

** Patients in this group were usually taking azathioprine and prednisone

A closer examination of the distribution of the periodontal parameters is displayed in Table 4 by categorizing the percent sites affected into relevant groupings. More than half of the patients presented with < 10% of sites with BOP, probing depth > than 4 mm, and gingival tissue that extended 3 to 4+ mm coronal to the CEJ (identified as (-) recession > 3mm or > 4mm). Few patients presented with (-) recession at > 10% of sites; the majority had no (-) recession. One quarter of the patients had (-) recession of 3 mm at up to 10% of examined sites. The percent of sites with visible plaque was equally distributed among the patients; 1/3 had < 10% of sites with visible plaque, 1/3 had 10-30%, and 1/3 had > 30% of sites with visible plaque.

Table 3. Summary statistics of clinical periodontal parameters in a sample of RTRs

% SITES WITH:	N	MEAN	MEDIAN
PII > 1	118	29.93	22.57
BOP = 1*	114	21.85	10
PD > 4*	114	14.8	5.87
CAL > 3*	114	27.25	22.8
CAL > 4*	114	12.51	4.65
CI > 1*	115	16.61	6.55
CI > 2*	115	8.82	0

* Clinical periodontal parameters were not measured on 4 participants, and calculus index was not assessed on 3 participants

Table 4. Distribution of categorized clinical periodontal parameters in a sample of RTRs

% SITES WITH:	FREQUENCY	PERCENT
PI > 1		
≤ 10% OF SITES	41	34
10 TO < 30% OF SITES	43	35
> 30% OF SITES	37	31
BOP = 1		
≤ 10% OF SITES	62	51
10 TO < 30% OF SITES	32	27
> 30% OF SITES	27	22
PD > 4		
≤ 10% OF SITES	78	64
10 TO < 30% OF SITES	25	21
> 30% OF SITES	18	15
CAL > 3		
< 10% OF SITES	34	30
10 TO < 30% OF SITES	42	37
> 30% OF SITES	38	33
(-) RECESSION > 3 mm		
0%	64	56
0 TO ≤ 10%	30	26
< 10%	20	18
(-) RECESSION > 4 mm		
0%	89	78
0 TO ≤ 10%	16	14
< 10%	9	8

The majority (68%) of the patients who were evaluated did not present with any signs of gingival enlargement, and 83% presented with little to no gingival enlargement at all. Eleven percent of patients had at least one site in one sextant with severe gingival

enlargement (Table 5). In the group with sites with severe enlargement, very few had generalized severe gingival enlargement. Sites of gingival enlargement were generally isolated to inter-dental areas of the buccal surfaces of the anterior dentition. Occasionally, however, the premolar area or the lingual gingival tissues were affected. Of the 39 patients who presented with some extent of gingival enlargement, only a few displayed enlarged tissue that included an entire sextant or arch.

Table 5. Prevalence and severity of gingival enlargement

	FREQUENCY	PERCENT
GE		
NO	81	68
YES	39	32
SEVERITY		
0	81	68
1	18	15
2	9	8
3	3	3
4	9	8

*Severity defined as: 0 = no gingival enlargement; 1 = mild gingival enlargement covering <1/3 of the clinical crown; 2 = moderate gingival enlargement covering 1/3 to ½ of the clinical crown; 3 = severe gingival enlargement covering 1/2 to 2/3 of the clinical crown; 4 = severe gingival enlargement covering 2/3 to the entire clinical crown

Bivariate analysis exploring GE in relation to demographic and clinical variables

The only demographic variable associated with GE is age. (Table 6) Among patients with gingival enlargement, 32% overall, most were between the ages of 26 and 45. Roughly 1/3 of those with gingival enlargement were over the age of 46 years old. However, 3 out of 4 of the patients between the ages of 18-25 showed signs of gingival

enlargement. Half of the patients between 26 and 35 and 20% of patients over the age of 46 showed signs of gingival enlargement. 30% of the Caucasian and African-American patients had some degree of gingival enlargement. 50% of the Hispanic patients and 16% of the Asian patients showed signs of gingival enlargement. When considering gender and gingival enlargement, there were a higher percentage of males who presented with signs of enlargement 38% of males vs. 27% of females.

Table 6. Prevalence of gingival enlargement by age, race, and gender

	GE PRESENT	GE ABSENT	P-VALUE*
AGE	N (%)	N (%)	
18-25	3 (75%)	1 (25%)	0.03
26-35	11 (50%)	11 (50%)	
36-45	12 (39%)	19 (61%)	
46-55	6 (20%)	24 (80%)	
56+	7 (21%)	26 (79%)	
RACE/ETHNICITY			
CAUCASIAN	14 (33%)	28 (67%)	0.10
ASIAN	4 (16%)	21 (84%)	
HISPANIC	15 (47%)	17 (53%)	
AFRICAN AMERICA	6 (28%)	15 (72%)	
GENDER			
MALE	24 (38%)	40 (62%)	0.24
FEMALE	15 (27%)	41 (73%)	

*** Fisher's Exact Test**

Whether we use a non-parametric approach or a conventional contingency table method, we found a strong association between GE and plaque, BOP, and sites with probing depths > 4 mm, and a calculus index > 1. (Table 7) Patients with gingival enlargement in at least one quadrant had visible plaque at twice as many sites, BOP at 4

times as many sites, and > 4 mm probing depths at 5 times as many sites as patients without gingival enlargement. There were no statistical differences between clinical attachment loss of > 3 or 4 mm, or a calculus index > 2. Among patients without gingival enlargement, roughly 80% had 0 to < 10% of sites affected by the previously mentioned parameters. The majority of patients with gingival enlargement tended to display a greater percent of sites that were affected by plaque, calculus, probing depth, etc. The opposite was noted among subjects without gingival enlargement. (-) recession was subdivided based on groups of 10% sites vs. 30-40% of sites for the other parameters, based on the low number of patients that presented with (-) recessions greater than 3 or 4 mm.

Table 7. Non-parametric bivariate analysis exploring GE in relation to periodontal parameters

% SITES WITH:	PRESENCE OF GE	N	MEAN	MEDIAN	MEDIAN 95% CI LOWER	MEDIAN 95% CI UPPER	P-VALUE*
PII > 1	NO	80	22.51	16.67	8.93	25	0.0001
	YES	38	44.55	41.37	17.26	60.9	
BOP = 1	NO	80	12.79	6.75	4.55	9.52	<0.0001
	YES	38	41.48	28.74	14.49	51.79	
PD > 4	NO	78	6.23	3.06	1.24	4.67	<0.0001
	YES	36	33.38	21.08	12.5	54.18	
CAL > 3	NO	78	26.98	22.78	17.86	26.54	0.78
	YES	36	27.85	20.5	7.69	30.86	
CAL > 4	NO	78	11.68	4.65	2.99	8.33	0.94
	YES	36	14.3	20.5	1.19	9.88	
CI > 1	NO	78	10.45	5.03	1.19	8	0.005
	YES	37	29.59	12	4.86	33.33	
CI > 2	NO	78	6.15	0	0	1.33	0.06
	YES	37	14.44	2.38	0	9.52	

***Mann-Whitney Test**

Table 9 summarizes a comparison of periodontal parameters among gingival enlargement severity groups. The amount of gingival enlargement was compared to the percent of sites that demonstrated the different periodontal parameters. A statistically significant association was found between the severity of gingival enlargement and visible plaque, BOP, probing depths > 4 and calculus. There was an increase in the percent of sites affected by each parameter when comparing no enlargement to the most severe enlargement noted. The relationship with clinical attachment loss was not statistically significant; all severity groups demonstrated about the same amount of attachment loss. Although calculus was found to be significantly associated with the severity of gingival enlargement, there was little difference among patients with a calculus index > 2 and the different severity groups.

Multivariate analysis of GE in relation to periodontal parameters

Overall, an increase in the probability of gingival enlargement was noted among patients with a higher percentage of sites with plaque, BOP, probing depth > 4 mm and (-) recession > 3 mm, compared to a reference group with fewer sites affected (Table 10). The odds ratios increase dramatically as more sites display the periodontal parameters. The use of calcium-channel blockers was also included in this evaluation and the results indicate that their use increases the probability of gingival enlargement as much as plaque does. The use of calcium-channel blockers was shown to increase the probability of gingival enlargement in each group. Odds ratios were particularly high, at least 10, for patients with > 30% of sites with BOP or probing depth > 4 mm or (-) recession > 3 mm.

Table 8. Prevalence of GE in relation to categorized periodontal parameters

% SITES WITH:	GE = 0	GE > 0	TOTAL	P-VALUE*
PI > 1				
≤ 10% OF SITES	32 (82%)	7 (18%)	39 (33%)	0.003
10 TO < 40% OF SITES	31 (74%)	11 (26%)	42 (36%)	
> 40% OF SITES	17 (46%)	20 (54%)	37 (31%)	
TOTAL	80 (68%)	38 (32%)	118 (100%)	
CI > 1				
0%	27 (79%)	7 (21%)	34 (30%)	<0.0001
0 TO ≤ 20%	40 (74%)	14 (26%)	54 (47%)	
> 20%	11 (41%)	16 (59%)	27 (24%)	
TOTAL	78 (68%)	37 (32%)	115 (100%)	
BOP = 1				
≤ 10% OF SITES	51 (88%)	7 (12%)	58 (51%)	<.0001
10 TO < 30% OF SITES	18 (58%)	13 (42%)	31 (27%)	
> 30% OF SITES	9 (36%)	16 (64%)	25 (22%)	
TOTAL	78 (68%)	36 (32%)	114 (100%)	
PD > 4				
≤ 10% OF SITES	62 (85%)	11 (15%)	73 (64%)	0.003
10 TO < 30% OF SITES	13 (54%)	11 (46%)	24 (21%)	
> 30% OF SITES	3 (18%)	14 (82%)	17 (15%)	
TOTAL	78 (68%)	36 (32%)	114 (100%)	
CAL ≥ 3				
≤ 10% OF SITES	20 (59%)	14 (41%)	34 (30%)	0.16
10 TO < 30% OF SITES	33 (79%)	9 (21%)	42 (37%)	
≥ 30% OF SITES	25 (66%)	13 (34%)	38 (33%)	
TOTAL	78 (68%)	36 (32%)	114 (100%)	
(-) RECESSION > 3 mm				
0%	55 (86%)	9 (14%)	64 (56%)	<.0001
0 TO ≤ 10%	21 (70%)	9 (30%)	30 (26%)	
> 10%	2 (10%)	18 (90%)	20 (18%)	
TOTAL	78 (68%)	36 (32%)	114 (100%)	
(-) RECESSION > 4 mm				
0%	73 (82%)	16 (18.0%)	89 (78%)	<.0001
0 TO ≤ 10%	5 (31%)	11 (69%)	16 (14%)	
> 10%	0 (0%)	9 (100%)	9 (8%)	
TOTAL	78 (68%)	36 (32%)	114 (100%)	

*** Fisher's Exact**

Table 9. Non-parametric bivariate analysis exploring GE severity in relation to periodontal parameters

% SITES WITH:	GE SEVERITY	N	MEAN	MEDIAN	MEDIAN 95% CI LOWER	MEDIAN 95% CI UPPER	P-VALUE*
PII > 1	0	80	22.51	16.67	8.92	25	<0.0001
	1	18	29.16	16.37	8.67	41.67	
	2	9	57.44	65.28	38.67	84.85	
	3	3	25.24	7.69	7.14	60.9	
	4	8	76.68	79.28	57.74	100	
BOP = 1	0	78	12.79	6.75	4.55	9.52	<0.0001
	1	17	20.42	17.86	5.13	28.57	
	2	9	40.79	44.93	10.26	81.6	
	3	3	70.04	100	10.12	100	
	4	7	81.29	94.31	27.08	100	
PD > 4	0	78	6.23	3.06	1.24	4.68	< 0.0001
	1	17	11.67	6.55	2.68	13.69	
	2	9	37.22	27.56	18.12	61.91	
	3	3	54.2	59.62	36.31	66.68	
	4	7	72.21	83.33	20.83	92.86	
CAL > 3	0	78	26.98	22.8	17.86	26.54	0.82
	1	17	22.6	16.68	5.36	30.86	
	2	9	30.29	11.91	1.92	75.36	
	3	3	39.99	52.11	1.19	66.67	
	4	7	32.29	24.22	4.17	83.33	
CAL > 4	0	78	11.68	4.65	2.99	8.33	0.60
	1	17	9.13	2.68	0.6	8.67	
	2	9	17.56	2.68	0	54.35	
	3	3	21.71	19.01	0.6	45.51	
	4	7	19.49	10.43	0.6	70	
CI > 1	0	78	10.45	5.03	1.19	8	0.01
	1	18	17.93	6.85	0	16.07	
	2	9	34.76	23.21	0	72.73	
	3	3	45.59	32.69	5.36	98.72	
	4	7	46.07	33.33	2.38	100	
CI > 2	0	78	6.15	0	0	1.33	0.04
	1	18	5.14	0	0	4.76	
	2	9	19.56	9.52	0	43.18	
	3	3	10.68	11.54	0	20.51	
	4	7	33.37	4.76	0	100	

*** Kruskal-Wallis Test**

Table 10. Multivariate models exploring the probability of GE in relation to periodontal parameters controlling of CA-blocker use

% SITES WITH:	ODDS RATIO	95% CI LOWER	95% CI UPPER	P-VALUE
PII > 1				
10 TO ≤ 40% vs. ≤ 10% OF SITES	1.98	0.62	6.37	0.25
>40% vs. ≤ 10% OF SITES	6.38	2	20.39	0.002
Ca CHANNEL BLOCKER USE	4.57	1.84	11.35	0.001
BOP = 1				
10 TO ≤ 30% vs. ≤ 10% OF SITES	6.45	1.96	21.18	0.002
≥30% vs. ≤ 10% OF SITES	20.23	5.46	75	<0.0001
Ca CHANNEL BLOCKER USE	5.54	1.95	15.75	0.001
PD > 4				
10 TO ≤ 30% vs. ≤ 10% OF SITES	4.78	1.61	14.25	0.005
≥30% vs. ≤ 10% OF SITES	24.91	5.78	107.45	<0.0001
Ca CHANNEL BLOCKER USE	3.78	1.37	10.39	0.01
(-) RECESSION > 3 mm				
0 TO ≤ 10% vs. 0 SITES	2.75	0.93	8.15	0.671
> 10% vs. 0 SITES	46.22	8.4	254.25	<0.0001
Ca CHANNEL BLOCKER USE	1.7	0.55	5.22	0.3533
(-) RECESSION > 4 mm				
(-) RECESSION > 4 mm	10.36	3.48	30.79	<0.0001
Ca CHANNEL BLOCKER USE	2.16	0.75	6.24	0.16

Discussion:

Improvements in post-transplantation medication regimens has decreased the mortality associated with renal transplants.[38] As the number of successful renal transplants increases, the likelihood of treating renal transplant patients in a dental setting also increases. It has long been established and shown that specific anti-rejection drug

therapy following renal transplantation is associated with gingival enlargement.[8,23] An understanding of this process is critical in the care of these patients and also for improved efficiency and efficacy of future studies into gingival enlargement within a post-transplant population.

As the number of renal transplant recipients increases, it is likely that the number of subjects involved in studies of these individuals will also increase. Current methods of assessing gingival enlargement are not difficult, but are time-consuming and may have the potential to add considerable expense to studies. One of the goals of this study was to determine if routine clinical periodontal parameters, that are already part of study protocols, could be used as accurate surrogates for the risk of developing gingival enlargement.

Conducting this study at a major transplant center allowed for relatively easy access to a diverse population of renal transplant recipients. This allowed for the recruitment of more subjects than have been included in previous studies of gingival enlargement in renal transplant recipients.[9,13,18,26] A total of 122 subjects were recruited for this study. Patients were recruited on two different days, one morning session and one afternoon session, to maximize variability of the subject pool. The analysis of sample characteristics in our study sample indicates that participants were equally spread with respect to age, gender, and race.

Overall, the subject population of this study presented with fairly good oral hygiene. Only about 10% of the total sites showed bleeding on probing and 20% had visible plaque at the gingival margin. Within this population, a few subjects accounted for the majority of the findings. This may account for skewed data and why median

values rather than mean values were used to more accurately describe the data pool. Few patients presented with plaque at the gingival margins, calculus, or bleeding on probing. A small proportion of the patients had extensive plaque accumulation and generalized gingival enlargement due to regular dental care for most of the patients, however, these data are not presented as part of this study and conclusions based on this information are only speculation.

The use of the drug tacrolimus®, which is not associated with gingival enlargement, will likely decrease the prevalence of gingival enlargement from previously reported rates of 13% to 85%.[14,30] In this study, however, the prevalence of gingival enlargement was found to be 32%, within the previously reported range of incidence.[9] As previously reported, there was no relationship found between gender, race, and the presence of gingival enlargement, but there was a statistically significant relationship between age and gingival enlargement ($p=0.025$). This association with increased age and gingival enlargement is in agreement with previous studies.[39,40] It should be noted, however, that other studies have not found this association with other medications associated with gingival enlargement.[41,42] There was no difference between males and females with respect to gingival enlargement, however, previous studies have stated that females are more likely to have gingival enlargement than males.[20,43]

The wide range in the prevalence reported by various investigators is very likely due to the variety of methods that are used to assess gingival enlargement. The use of photographs or study casts allow for the objective measurement of enlarged tissues, via the use of rulers or graduated probes.[44-46] A potential limitation of the method used in this study is that it is based on a visual interpretation of the extent of gingival

enlargement and thus subject to individual interpretation of the examiner. Multiple examiners, in an attempt to standardize the assessments, did initial evaluations, however, one examiner completed later assessments. The benefit of the method used in our study was the fact that assessments took no more than one minute to complete and only required a mouth mirror and an overhead light source. As a result, more patients were evaluated and the end result was similar to previous studies.[9] The acceptance of more simple methods of assessment will allow the evaluation of larger groups of subjects and an increase in power of the studies, hopefully allowing for stronger conclusions concerning questions about gingival enlargement in renal transplant patients.

Among the patients who presented with any gingival enlargement, the majority had only minor, localized gingival enlargement. As shown in previous studies, the most severe enlargement was isolated to the maxillary premolar and anterior teeth and mainly involved the interdental papilla.[18,47] Gingival enlargement was rarely noted on the straight buccal surface of the teeth, however, the interproximal tissue occasionally did enlarge to cover the straight buccal surfaces, as was also shown in previous reports. [18,47]

A correlation between periodontal parameters and gingival enlargement was shown in a recent smaller study and was confirmed within the population of this study.[13] Plaque, calculus, bleeding on probing, and probing depths > 4 mm were each shown to be associated with the presence of gingival enlargement. There was, however, no significant association noted between clinical attachment loss > 3 mm and gingival enlargement. This is in agreement with previous studies that reported that the presence of bacteria at the gingival margin, in the form of plaque, was a factor in gingival enlargement.[8,27,48]

Probing depth and not attachment loss was found to be related to gingival enlargement in this study. Deeper probing depths are more difficult to maintain and may predispose the patient to bacterial accumulation that may eventually stimulate gingival enlargement[9]. It is possible to have attachment loss without significant probing depth, for example, in the presence of gingival recession. I n this situation, the patient can more easily maintain the area and gingival enlargement may be minimized.[12,49]

As plaque, calculus, probing depth, or bleeding on probing increased so did the percent of sites affected with gingival enlargement. Higher rates of bleeding, plaque, and calculus have been shown to increase the risk of developing gingival enlargement.[26] As the amount of tissue above the CEJ increased, so did the amount of gingival enlargement. Once again, few sites were affected, but affected sites were more difficult to maintain which lead to more plaque accumulation and the development of gingival enlargement.

This study demonstrated a higher incidence of gingival enlargement in the presence of several periodontal factors. As the percent of sites with deeper probing depths, bleeding on probing, plaque, or gingival margins located > 3 above the CEJ increased, the odds of presenting with gingival enlargement also increased dramatically. As the number of potential sites that can harbor bacteria increases, the odds of developing gingival enlargement should also increase. A six-fold increase in the odds of developing gingival enlargement was noted in patients with probing depths > 4 mm and a 20-fold increase for patients with excess tissue above the CEJ when compared to patients with minimal probing depths or no tissue over the CEJ. A significant increase in the odds of developing gingival enlargement was also noted in patients who presented with generalized bleeding on probing. Bleeding on probing, a marker for inflammation,

should be expected to increase because part of gingival enlargement is due to inflammation.

Clinical attachment loss, probing depth, the calculus index, and the plaque index were not considered together in a single analysis model because of their inter-relationship. A strong association with gingival enlargement suggests that the strongest determinant of enlargement in not simply the use of a particular medication, cyclosporin in this case, but the presence of multiple periodontal etiologic factors. Dosage may also be an important factor in the development of gingival enlargement. Dosages greater than 500 mg per day have been shown to induce gingival enlargement.[40] In fact an initial evaluation of our data revealed that the use of both Tacrolimus® and or cyclosporin was not related to gingival enlargement when a comparison was made between patients on these medications versus patients who were not. This finding is in agreement with previous studies that reported that tacrolimus was not associated with gingival enlargement, but it is not in agreement with respect to cyclosporin use.[14] The use of a calcium-channel blocker, however, was shown to be associated with gingival enlargement which also in agreement with previous studies.[49,50] Within the population studied here, the use of a calcium-channel blocker, was shown to increase the odds of gingival enlargement between two and six times. A preliminary evaluation of the data revealed a significant association between gingival enlargement and calcium-channel blockers that led to its inclusion on future analyses. This finding not only confirms the importance of calcium-channel blockers in the development of gingival enlargement, but it also shows their effect in relation to cyclosporine. Although it is known that the combination of these two medications results in more pronounced enlargement, it may be

that the calcium-channel blocker is actually more important in this development, especially in conjunction with periodontal factors.[8]

The results of this study may be useful to improve the design of future studies investigating drug-influenced gingival enlargement. The data presented here show significant associations between the data that are collected as part of routine periodontal evaluations and gingival enlargement. Maximizing the use of data that is normally collected may allow for a streamlining of investigations and, therefore, a reduction in study time and cost. In lieu of study casts, photographs, or visual evaluations, periodontal data could be used to assess gingival enlargement. This change could allow for the inclusion of more subjects and stronger conclusions about drug-influenced gingival enlargement. It may also be possible to develop an algorithm that translates some of the periodontal parameters into a measure of gingival enlargement. This would provide an objective method of measuring gingival enlargement that is reproducible by multiple examiners. It may also aid in determining a more accurate estimate of the prevalence of gingival enlargement among patients on immunosuppressive medications.

In addition to possible changes in study protocols, the data collected in this study could be used to develop treatment protocols for renal transplant patients. It is clear that patients on immunosuppressive therapy and calcium-channel blockers are at risk for developing gingival enlargement. Gingival enlargement may severely and negatively impact the lives of these individuals. Treating gingival enlargement is also very difficult and often ineffective, therefore, developing measures to prevent gingival enlargement would be beneficial in this population. Oral evaluations prior to transplant surgery can identify patients with plaque, calculus, bleeding on probing, and deeper probing depths.

Once identified, tailored periodontal therapy and oral hygiene improvements may alter the development of gingival enlargement once immunosuppressive therapy begins.

Due to the cross-sectional design of this study, it cannot be determined if plaque is a contributing factor in the development of gingival enlargement or a result of it. We can say that the two are related, but future studies need to be designed to answer this question. Prospective studies that begin before the time of transplant surgery and prior to immunosuppressive therapy should help to determine the actual role of plaque and other periodontal parameters in the development and progression of gingival enlargement.

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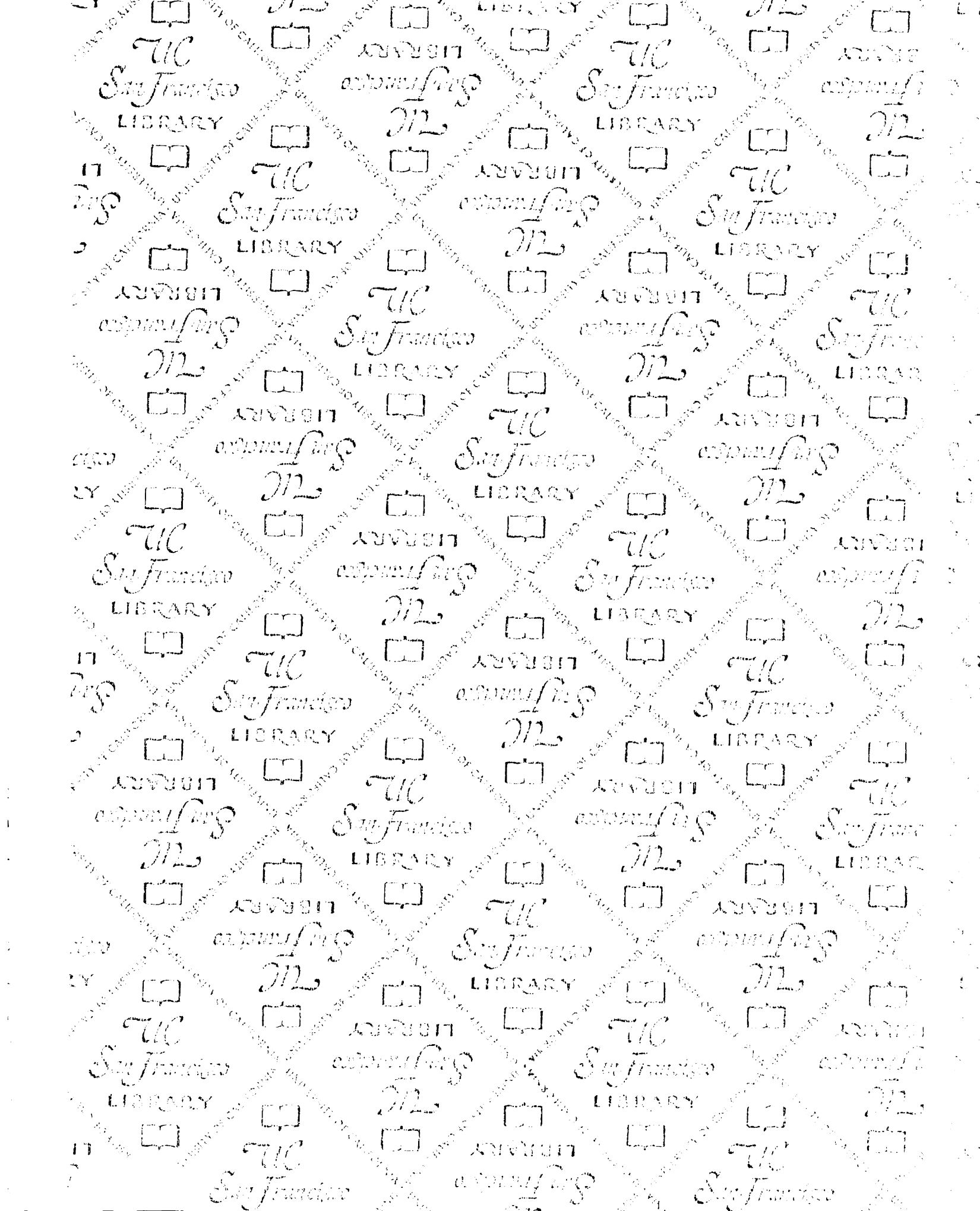
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