Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

GINGIVAL HYPERPLASIA IN PATIENTS WITH RENAL PATHOLOGY

Madrid, academic year 2022/2023

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SUMMARY AND KEYWORDS

Introduction: Renal replacement therapy is the preferred treatment for patients with chronic kidney disease. Indeed, Immunosuppressive therapy is required for the transplanted patient throughout his life to avoid the risk of rejection. The most typical maintenance immunosuppressive regimen for kidney transplant recipients is based on calcineurin inhibitors such as Cyclosporine-A. Drug-induced gingival hyperplasia is a common condition which can be observed in patients taking immunosuppressive therapy such as Cyclosporin-A following organ transplant surgery. Pain is frequently brough on by the patient, as it compromises the aesthetic, occlusion, phonation, and oral hygiene maintenance of the patient. Several treatment alternatives can be used to manage gingival hyperplasia in renal patients and can be categorized as non-surgical and surgical therapies. **Objectives:** The aim of this thesis is to determine the main clinical features and risk factors associated to gingival hyperplasia and the dental management of the renal patient. **Methodology:** To create this thesis, numerous studies and clinical cases were screened and selected from scientific databases such as PubMed, Medline, Academic Search Ultimate, Web of Science and Google Scholar. 100 articles were examined, of which 25 remained after applying the exclusion criteria. **Results**: Studies have shown that different treatment therapies such as the drug substitution, periodontal therapy, photodynamic therapy, surgical procedures and laser therapy have been effective in the reduction or elimination of gingival hyperplasia. **Conclusion** : The exact histopathological mechanism of medically-induced gingival hyperplasia is still unknown and more investigation need to be performed. The goal of the treatment is to return to a physiological healthy gingival status comfortable for the patient by the mean of a correct diagnosis and different types of therapies.

Keywords: Dentistry, Gingival hyperplasia, renal patient, Cyclosporin-A, Dental management

RESUMEN Y PALABRAS CLAVES

Introducción: El trasplante renal es el tratamiento preferido para los pacientes con enfermedad renal crónica. Debido a este tratamiento, se requiere una terapia inmunosupresora para el paciente trasplantado para evitar el riesgo de rechazo. El régimen inmunosupresor más típico para los pacientes trasplantados de riñón se basa en inhibidores de la calcineurina como la Ciclosporina-A. La hiperplasia gingival inducida por fármacos es una afección que puede observarse en pacientes que reciben tratamiento inmunosupresor como ciclosporina-A tras una intervención quirúrgica de trasplante de órganos. Es habitual que estos pacientes tengan dolor crónico, además de compromiso estético, alteraciones en la oclusión, fonación y mantenimiento de la higiene oral del paciente. Tenemos varias alternativas de tratamiento para manejar la hiperplasia gingival que se pueden clasificar como terapias no quirúrgicas y quirúrgicas. **Objetivos:** Determinar las principales características clínicas y factores de riesgo asociados a la hiperplasia gingival y el manejo odontológico del paciente renal. **Metodología**: Para este trabajo de fin de grado, se han cribado y seleccionado numerosos estudios y casos clínicos de bases de datos científicas como PubMed, Medline, Academic Search Ultimate, Web of Science y Google Scholar. Se examinaron 100 artículos, de los que quedaron 25 tras aplicar los criterios de exclusión. **Resultados:** Los estudios han demostrado que diferentes terapias de tratamiento como la sustitución de fármacos, la terapia periodontal, la terapia fotodinámica, los procedimientos quirúrgicos y la terapia con láser han sido eficaces en la reducción o eliminación de la hiperplasia gingival. **Conclusión**: Aún se desconoce el mecanismo histopatológico exacto de la hiperplasia gingival inducida por fármacos por lo que será necesario realizar más investigaciones. El objetivo del tratamiento es devolver al paciente un estado gingival fisiológicamente sano e indoloro mediante un diagnóstico correcto y diferentes tipos de terapias.

Palabras clave: Odontología, Hiperplasia gingival, Paciente renal, Ciclosporina-A, Tratamiento dental, gestión odontológica.

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1 INTRODUCTION

The regulation of body fluid osmolarity, excretion of metabolic waste, hormone production, and water and electrolyte homeostasis are all functions performed by the kidneys, crucial organs in the human body. (1) An adult patient that has a glomerular filtration rate of less than 60 ml/min/1.73 m2 or structural alteration of the kidney is considered as affected by chronic kidney disease. This clinical condition is characterized by its irreversibility and chronic progression caused by a permanent change in the structure or function of the kidneys. (2)

According to the glomerular filtration rate, chronic kidney disease can be classified as: (Table1)

Table 1. Chronic kidney disease according to glomerular filtration rate. (2)

Stages	Glomerular filtration rate values ml/min/1,73m2	Classification
Stage I	>90	Normal or high
Stage II	60-89	Slightly decreased
Stage III A	45-59	Mild to moderate decreased
stage III B	30-44	Moderate to severely decreases
Stage IV	15-29	Severely decreased
Stage V	<15	Kidney failure

Related to this pathology, several treatment options exist as the hemodialysis or the peritoneal dialysis which objectives are to restore the electrolyte balance and maintain and adequate pH by withdrawing solutes and water. The treatment by dialysis consists of blood passing through an extracellular circuit thanks to a vascular access. Peritoneal

dialysis is considered as a continuous therapy as it provides a great portability and less restrictive diet while removing solutes and water from the renal patient's body, allowing the preservation of the renal function. This therapy provides a great autonomy to the renal patient but it implies also great responsibilities as peritoneal dialysis needs to be carried out every day. This therapy allowed to improve the conditions of life of the renal patient, however complications related to infectious processes, structural changes in the peritoneal membrane or to the metabolism need to be anticipated and controlled as the can compromise the effect of the treatment. (3) Indeed, renal replacement therapy is the preferred treatment for those with chronic or end-stage kidney disease, since it provides the highest survival rate and quality of life. (4)

Immunosuppressive therapy is required for the transplanted patient throughout his life to avoid the risk of rejection and prevent the renal graft to be exposed to cellular alterations as a consequence of the recipient's acute immune response to the transplanted organ, which can lead to the loss of the graft. (5) Although the beneficial effect of immunosuppressive treatment on graft survival has been proven, these drugs have a verry narrow therapeutic range. Existing immunosuppressant prescribing practices should be more carefully analyzed and specified since the number of elderly patients receiving renal transplantation keeps rising. It is crucial to determine how aging impacts the pharmacokinetics and pharmacodynamics of immunosuppressive medications in order to create the safest and most effective immunosuppressive regimen. (6) A good knowledge from the care team in charge of the patient of its potential adverse effects is required due to the various application of this therapy such as in transplantation medicine, nephrology and other fields. (7)

The most typical maintenance immunosuppressive regimen for kidney transplant recipients consists of a triple therapy, which combines a calcineurin inhibitor (Cyclosporine or Tacrolimus), an antimetabolite (Mycophenolate or Azathioprine), and a corticosteroid (Prednisolone or Prednisone). Due to modifications in medication pharmacokinetics and pharmacodynamics, the difficult balance between under and over-immunosuppression becomes more complicated in elderly receivers when compared to younger people with similar features. (6)

Introduced in the 1980's as an immunosuppressant, Cyclosporine-A is one of the most frequently efficient immunosuppressive therapy used in organ transplantation cases since its miracle discovery by Borel in 1972. It is a cyclic polypeptide isolated from the Tolypocladium inflatum fungus widely used for prevention of transplant rejection as well as for the treatment of diseases like rheumatoid arthritis, multiple sclerosis, psoriasis, pemphigus vulgaris and other immunological diseases. (8) Cyclosporine-A is extensively metabolized by hepatic cytochrome P3A to produce more than 25 metabolites, with the biliary system accounting for 90% of its excretion. Since Cyclosporine-A strongly binds to red blood cells, whole blood concentrations are frequently used to analyze medication levels. Numerous variables, including drug interactions, patient weight, time post-transplant, patient hepatic function and hematocrit, have all been related to the significant heterogeneity in Cyclosporin-A pharmacokinetic. (6)

It allowed an increase in the number of transplants and their survival. However, the widespread clinical use of Cyclosporin-A has been questioned for its numerous side effects such as nephrotoxicity, hepatotoxicity, arterial hypertension and gingival overgrowth. (6) Tacrolimus is currently substituting it in usage as it has a similar immunosuppressant effects and lower susceptibility to produce side effects such as medically-induced gingival hyperplasia. (8)

Cyclosporin-A induced Gingival hyperplasia was first observed by Calne et al in 1981 and documented by Rateitschak–Pluss et al and Wysocki et al in 1983 in renal recipients. (8-9) Gingival enlargement or gingival overgrowth is the preferred term for all medically-induced gingival lesions previously termed gingival hyperplasia or gingival hypertrophy. Three main groups of drugs can produce this pathology as a side effect: anticonvulsants, calcium channel blockers such as Amlodipine frequently associated to immunosuppressive drugs and immunosuppressants especially cyclosporin-A. (10)

Drug-induced gingival hyperplasia is a common condition which can be observed in patients taking immunosuppressive therapy such as Cyclosporin-A following organ transplant surgery, with lower incidence in patients taking tacrolimus and usually observed after three months of drug consumption. (11-12) Based on the literature available, Gingival hyperplasia occurs in about 30% of cyclosporine-treated patients with a prevalence ranging from 6% to 81%. (6) Discomfort pain and complaints are frequently

brough on by the patient, as it is compromising the aesthetic, occlusion, phonation, and oral hygiene maintenance of the patient as shows figures 1 and 2. (7,10)

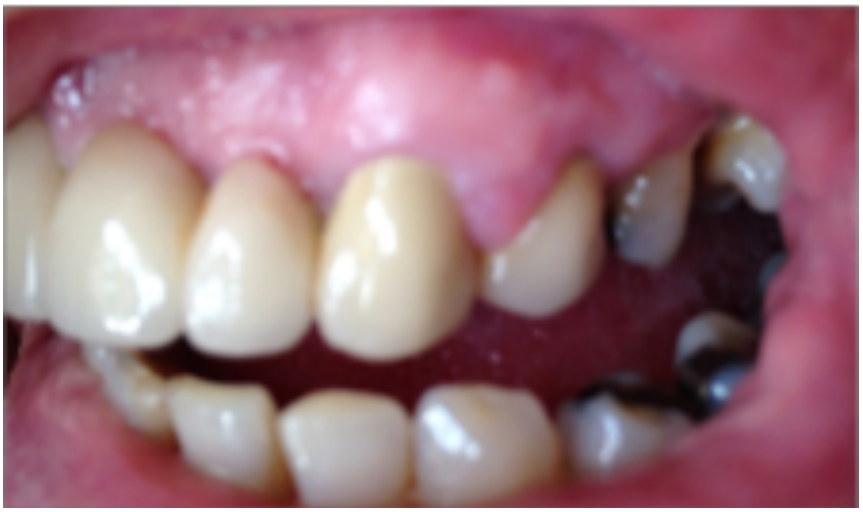

Figure1. Photograph showing Cyclosporin-induced gingival hyperplasia. (9)

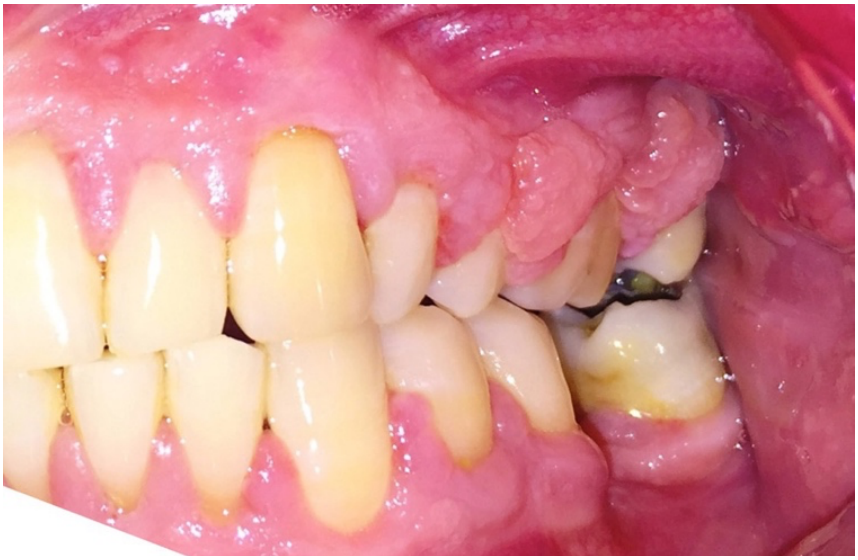

Figure2. Photograph showing Cyclosporin A and amlodipine-induced gingival hyperplasia. (8)

According to Bokenkamp and Bohnhorst, gingival overgrowth can be classified as: (Table 2)

Table 2. Bolenkamp and Bohnhorst gingival overgrowth classification (1994). (13)

Grade 0	No signs of gingival overgrowth
Grade 1	Gingival hyperplasia confined to interdental papilla
Grade 2	Hyperplasia in interdental papilla and marginal gingiva
Grade 3	Gingival hyperplasia covering at least ¾ of tooth crown

The exact pathogenic mechanism of Cyclosporin-induced gingival hyperplasia is still unprecise. It was suggested that the long-term use of the drug may have direct or indirect consequences on gingival fibroblasts and collagen metabolism. (9)

Understanding the biological mechanism of periodontal disease and the immunological status of kidney transplant recipient is crucial. (13)

Based on the patient's medical history and an intraoral examination, the diagnosis is simple. (10) Several treatment alternatives can be used to manage gingival hyperplasia in renal patients; they can be categorized as non-surgical and surgical therapies. (12)

All of the treatment options have been used to either decrease or get rid of gingival enlargement and associated pockets. As long as gingival overgrowth is treated, maintaining proper dental hygiene and scheduling regular checkups is essential to achieving greater and more consistent results. (10)

Through correct diagnosis, treatment, and with patient’s cooperation, complex systemic dental pathologies such as drug-induced gingival hyperplasia can be managed in a conservative way without invasive surgeries to reach a stable and healthy periodontal status. (1) In more severe cases, laser therapy or surgery may be indicated.

Renal graft is the most efficient therapy for patient affected by chronic kidney disease, regarding its survival rate and the subsequent quality of life that it provides. Therefore, renal transplant patients need to take immunosuppressive therapy throughout their entire lives to prevent the transplanted organ from being rejected. What are the

different treatment options and the dental management regarding renal transplanted patient affected by medically-induced gingival hyperplasia?

2 OBJECTIVES

This review aims to study gingival hyperplasia as a side effect of immunosuppressive therapy in renal patients.
Therefore, the objectives addressed are the following:

-To understand how 1st intention immunosuppressive therapy in renal-transplanted patient can affect the oral health producing gingival hyperplasia.

-To determine the main clinical features and risk factors associated to medically-induced gingival hyperplasia and how it can affect the renal patient functionally and esthetically.

-To define the short and long-term dental management of renal patients affected by medically-induced gingival hyperplasia.

3 MATERIALS AND METHODS

The purpose of this graduation project was to produce a recent and actualized review of renal patients affected by medically-induced gingival hyperplasia, as a side effect of immunosuppressive therapy. For this aim, electronic data bases such as PubMed, Medline, Academic search ultimate, Google scholar, dentistry and Oral Science Sources and Web of Science, CRAI library of Universidad Europea were used to search scientific publications published in the last 5 years.

The key words and Boolean operators used for this review were the followings: "Dentistry", "Gingival hyperplasia", "Gingival hyperplasia" AND "renal patient", "Renal patient" AND "Cyclosporin A", "Renal patient "AND "Dental management".

After the application of my inclusive and exclusive criteria's, 25 articles were extracted to be used in this review, with a publication date range of between 2018-2022.

Only publications written in English or Spanish were used to perform this review.

Inclusion criteria:

- Languages: English, Spanish.
- Year of publication: less than 5 years.
- Type of sources: Scientific articles, journals and case reports.

Exclusion criteria:

- Not related to oral health.
- Published more than 5 years ago.
- Outcome not related to renal pathologies.
- Articles written in another language than English or Spanish.

Table 3. PICO chart (Population, intervention, comparison, outcome)

Population	Patients affected by renal pathologies undergoing drug-induced gingival hyperplasia.
Intervention	Immunosuppressive therapy after renal transplantation.
Comparison	Different treatment options including surgical and non-surgical therapies.
Outcome	Affects stomatognathic apparatus in function and esthetic.

4 RESULTS

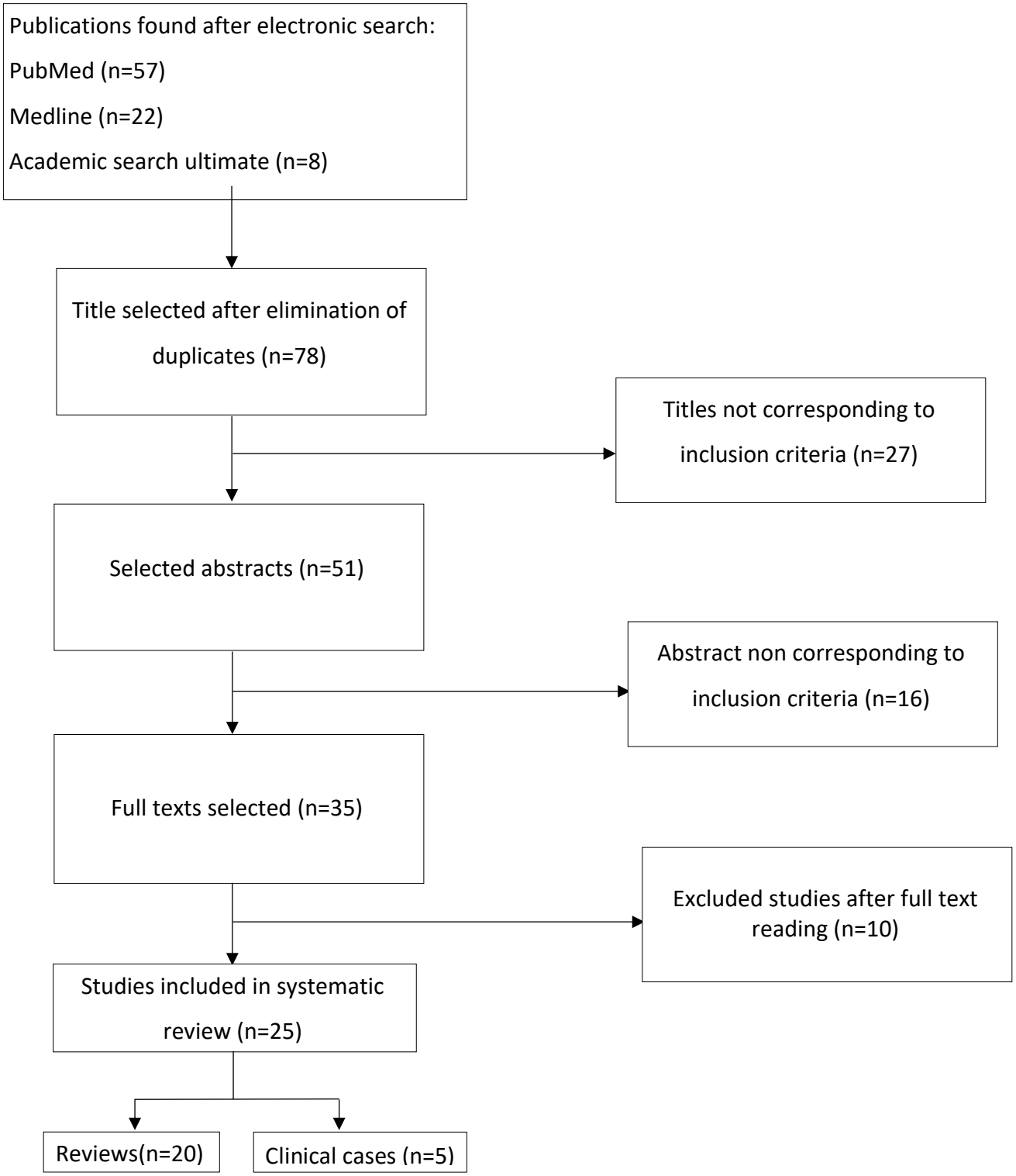

Figure3. Flowchart of the included studies

Table 4. Data collection table

Authors	Material & methods	Study	Results
Tillmann F-P, Harth A, Özcan F, Jörres A.	1 case Female 66 years old	Gingival hyperplasia induced by Cyclosporin A	Complete remission after the interruption of the treatment
Nivethitha K, Ramesh A, Talwar A, Shenoy N.	1 case Renal transplanted 21 years old male	Analysis of gingival hyperplasia induced by Tacrolimus	Dental management and treatment
Malek R, El Houari B, Kissa J.	1 case Renal transplanted woman 21 years old taking Cyclosporin-A, Prednisolone and Mycophenolate Gingival hyperplasia for 12 months	Non-surgical management of drug-induced gingival hyperplasia	- Gingival hyperplasia induced by Cyclosporin-A with associated periodontal pathology (Stage II, Grade B) -Produces discomfort, esthetic problems, difficulties for plaque control - Importance of periodontal therapy - 2 months: improvement of periodontal parameters

			and decrease of the inflammation. - supportive therapy every 2 months - Result of the treatment: complete elimination of gingival hyperplasia without an increase of the gingival index. - Clinical and radiological evaluation after 2 years: healthy gingiva
Rapone B, Ferrara E, Santacroce L, Cesarano F, Arazzi M, Liberato LD	72 renal transplanted patients	-Gingival hyperplasia incidence & prevalence induced by Cyclosporin and Tacrolimus in correlation with periodontal health status -Effect of immunosuppressive therapy associated with calcium channel blockers	-Lower incidence in patients treated with Tacrolimus. - Higher prevalence in patients treated with Cyclosporin A. - Importance of periodontal health

Damdoum M, Varma SR, Jaber MA, Nambiar M	1 case Female 68 years old with gingival enlargement and pain during mastication	Necrotizing ulcerative gingivitis as a complication of drug-induced gingival hyperplasia	-Gingival hypertrophy and pain during mastication - Biopsies have confirmed the diagnosis. -Several treatment interruptions of the treatment. Recurrence despite complete exodontia of the mouth
Lauritano D, Moreo G, Limongelli L, Palmieri A, Carinci F.	Human gingival fibroblasts culture in DMEME medium	Level of genes expressions	Genes expression is dysregulated
Lauritano D, Palmieri A, Lucchese A, Di Stasio D, Moreo G, Carinci F	Fibroblasts simulation by injection of cyclosporine solution	Gene expression profile of human fibroblasts	Genes expression is dysregulated
Candotto V, Baj A, Beltramini G, Scarano A, Palmieri A.	Incubation in cyclosporin solution of gingival tissular fragments from	Alteration of the inflammatory response by Cyclosporin	Cyclosporin has no effect on the inflammatory process in gingival fibroblasts

	healthy volunteers		
Aboujaoude S, Aoun G, Majzoub Z.	Prospective pilot study 20 patients: -7 patients taking Cyclosporin in syrup -13 patients taking Cyclosporin in capsule	Local and systemic effect of cyclosporin over gingival overgrowth severity - Assessed in all patients: Gingival growth, papillary bleeding, plaque index, gingival indices.	- Different effect according to the route of administration - Study refers the importance of dental plaque as a co-factor of gingival overgrowth - Plaque accumulation acts as a reservoir for gingival inflammation
Casu C, Murgia MS, Orrù G, Scano A.	1 case 18 Years old female taking Cyclosporin Gingival hyperplasia with bleeding on probing	-Photodynamic therapy with LED associated to a curcuma longa-based photosensitizer as treatment for medically-induced gingival hyperplasia -Objective: reduce the inflammation	- Method: 1 appointment and 30 seconds of application for each interdental papilla -Effectiveness of the treatment without recurrence. - Improvement after 1 cycle of photodynamic therapy.

		and bacterial load	- No edema or inflammation clinically detected
John K, Mishra AK, Gunasekaran K, Iyyadurai R.	1 case 19 years old male with stage 5 chronic kidney disease	Gingival hyperplasia induced by Amlodipine	Rare phenomenon, unknown mechanism
Liu Y, Peng Q, Liu B, Wang Z, Cao Q.	2 cases -42 years old renal transplanted male taking Tacrolimus and Felodipine -67 years old female	Initial periodontal surgery combined with surgery	Effectiveness of the treatment with good tolerance
Teshome A, Girma B, Aniley Z.	Meta-analysis and systematic review - 4 electronic databases were used: Medline, EMBASE, CINAHL and Cochrane Library	Efficacy of Azithromycin over Cyclosporine-induced gingival hyperplasia - Parameters: gingival growth index, plaque index, bleeding	- Clinical effectiveness of Azithromycin over gingival hyperplasia - Positive effect on the prevention of bacterial infection, gingival inflammation and bleeding on probing

	- RevMan 5.3 software used for statistical analysis - 5 randomized controlled trials and 167 eligible participants	and probing depth - 2 groups: one undergoing Azithromycin therapy and the other one with placebo or another antibiotic	

Different types of studies have been performed to understand the histopathological mechanism, clinical manifestations and the treatment options related to drug-induced gingival hyperplasia in renal patients.

Results were obtained by studies over human gingival fibroblasts cultures, meta-analysis, prospective pilot study and study of cases all related to medically-induced gingival hyperplasia.

As revealed by studies over human gingival fibroblasts, there is a direct correlation between medication such as Cyclosporin or Tacrolimus and the affectation of the gingival tissue. Indeed, immunosuppressive therapy and calcium channel blockers used in renal transplanted patients have a direct cellular effect on gingival fibroblasts affecting the inflammatory response and the gene expression but also producing endoplasmic reticulum stress. Several processes have been suggested such as the increase of the collagenous and non-collagenous gingival cellular components, the fibroblasts proliferation and the decrease of their apoptosis but also an imbalance of the cytokines.

Study of cases have shown that different treatment therapies such as the drug substitution, periodontal therapy, photodynamic therapy, surgical procedures and laser therapy have been effective in reducing and eliminate gingival hyperplasia.

5 DISCUSSION

5.1 Histopathological mechanism over gingival fibroblast

The most important cellular component of gingival connective tissue are the fibroblasts, that are in charge of different functions such as extracellular matrix secretion, regulation of the interstitial fluid and maintaining the structural integrity of the tissue. The administration of anticonvulsants, calcium channel blockers and immunosuppressants may result in drug induced gingival hyperplasia, characterized by fibroblasts hyperproliferation and deposition of extracellular matrix. (14) The buccal gingiva is permanently exposed to thermal, mechanical and chemical aggressions inducing a continuous renewing of the inflammatory cells and mediators as well as the fibroblasts and the disbalance between the oral microbiota and proinflammatory as well as anti-inflammatory mediators are important factors that need to be taken into account for the understanding of the histopathological mechanism of drug-induced gingival hyperplasia. Indeed, the administration of immunosuppressive drugs such as Cyclosporin-A weaken the host immune system as well as favorizing the increase of the dysbiosis and the heterogeneity of the oral microbiota. The dysregulation of the immunity response mechanism will influence the growth and the extent of medically-induced gingival hyperplasia. This condition represents the pathological expression of the effects of the medication and the mechanical stimuli over the gingiva but thanks to the innate immune response, the gingiva has developed biological mechanism such as the prevention of the gingival fibrotic hyperproliferation that represents an important mechanism in the prevention of medically-induced gingival hyperplasia in renal patients. (15)

Nowadays, the exact mechanism of drug induced gingival hyperplasia in renal patients is still unclear, but is based on the interaction between Cyclosporine A metabolites and the cellular components of gingival connective tissue, activating several defense mechanisms and cascades as well as producing different types of clinical manifestation. (9,10)

According to the literature, several theories have been suggested.

One of the most important events in drug-induced gingival hyperplasia is the deposition of the extracellular matrix, which results from a favorable balance between the synthesis and breakdown of extracellular matrix components. The extracellular matrix may experience greater fibrotic response as a result of cyclosporine A-induced inflammation. Inflammation may be necessary to encourage the beginning of the fibrotic process, although it is unrelated to its progression. (15,16)

High level of inflammation and low level of fibrosis are characteristics of gingival hyperplasia in association with immunosuppressive therapy. (14) Given that Cyclosporine metabolites have a direct impact on gingival fibroblasts, protein synthesis, and collagen production, one theory is that the buildup of gingival fibroblasts is caused by the prevention of cellular components apoptosis. (11) The authors hypothesized that in the pathophysiology of Cyclosporin-A induced gingival hyperplasia, reduced apoptosis may play a more significant function than enhanced cell division. The decrease of caspase-3 and keratinocytes apoptosis are both important factors related to gingival hyperplasia in renal patients. But on the other hand, according to Alaaddinoglu et al., the degree of keratinocyte apoptosis in the gingiva of kidney recipients with Cyclosporin A-associated GO is comparable to that seen in the inflamed gingiva of healthy people. (17)

The interaction of oral microorganisms with elements of the human immune system is what causes the development of gingival hyperplasia. Its progress is heavily influenced by chemokines and cytokines, whose receptors release inflammatory mediators. (15,18) As a consequence, the administration of Cyclosporin-A has several consequences at cellular level such as the alteration of the transcription of several cytokines, growth factors, interleukins and inhibiting T-cell production leading to an exaggerated innate immune response. (14,15,16) The interaction with cyclosporin-A produces an increase of proinflammatory and fibrogenic cytokines leading to a higher level of collagen and glycosaminoglycans synthesis reducing collagen breakdown and interfering with the production and function of matrix metalloproteinase, responsible for the conversion of collagenase precursor into mature collagenase. This will lead to the accumulation of connective tissue and matrix. (10,12, 17)

The inhibition of the transcription produced by Cyclosporin-A is related to the process of heterodimeric complex formation induced by the relationship between the drug and

its cytoplasmic receptor protein cyclophilin, inhibiting its phosphatase activity by binding to calcineurin and the expression of nuclear regulatory proteins. It results in the alteration of the transcription of several cytokines such as transforming growth factor-β1, interleukin-6 and 8 and fibroblast growth factors. (14)

Cyclosporine-A seems to induce a phenomenon called epithelial-mesenchymal transition. It is a process in which epithelial cells contacts are weakened and get the characteristics of the mesenchymal cells. The decrease of E-cadherin production is also a sign of epithelial-mesenchymal transition. (14)

Also, some authors suggested that genetic predispositions and interindividual susceptibility may play a role in the histopathological mechanisms of drug-induced gingival hyperplasia in patients affected by renal pathologies. Indeed, drug metabolizing enzymes may be altered due to cytochrome P450 polymorphism, which is considered as a factor of interindividual variability. (11,12)

5.2 Clinical features associated to drug-induced gingival hyperplasia

Drug-induced gingival hyperplasia usually stars clinically manifesting within 1 to 3 months after the initiation of the immunosuppressive therapy, reaching a plateau phase around 12 months. (14). Different parameters such as the grade of gingival overgrowth, the degree of inflammation, the consistency, the color and the location need to be analyzed. Also, the degree of gingival thickening (horizontal enlargement) and the extent of encroachment (vertical enlargement) of the gingival tissues on the labial and lingual aspects of adjacent tooth have to be taken into account during the intraoral examination. The clinical features of drug-induced gingival hyperplasia can be classified as localized or generalized and mild to severe affection depending on its extension and the type of gingiva that is affected. (10,12)

Due to modifications in medication pharmacokinetics and pharmacodynamics, the difficult balance between under and over-immunosuppression becomes more complicated in elderly receivers when compared to younger people with similar features. (6)

the overgrowth of gingival connective tissue consists in a pathological diffused or local growth of marginal and attached gingiva or interdental papilla. (14) Drug-induced gingival hyperplasia typically affects the vestibular surface of the gums more frequently and is initially seen in the interdental papillary region before spreading to the posterior regions. (8,14) The gingiva stars growing in heigh toward the occlusal or incisal surface of the crown followed by an increase in gingival thickness toward the bucco-lingual area extending more and more on the surface of the clinical crown. (10) The growth begins as a painless, bead-like expansion, but as the disorder worsens, it may turn into a huge fold. Interdental papilla has more susceptibility to nodular enlargement than other parts of the gingiva that may be related to the difference in cellular and molecular composition. (8,14)

The consistency can be firm or tender on palpation, associated or not with bleeding with a color evolution form pink to purplish-red. (9,18)

Despite the clinical signs and symptoms of gingival hyperplasia associated to medication appear to be similar, it has been shown that tissues affected by Cyclosporin-A are typically more hyperemic and bleed more readily upon probing, showing higher level of inflammation. (10)

Gingival hyperplasia may lead to severe complications for the dento-maxillary apparatus such as difficulties in the phonation, pain and discomfort, affectation of the occlusion and the esthetic. (21) Also, this condition can compromise the correct maintenance of the oral hygiene as it facilitates the retention of bacterial plaque and potentially affect the periodontal health status leading to tooth loss. (14,18)

5.3 Risk factors associated to drug-induced gingival hyperplasia

The gingiva is exposed to thermal, mechanical and chemical factors throughout renal patient's life as well as it undergoes a continuous renewing of the inflammatory cells. (15)

The pathogenesis of drug-induced gingival hyperplasia can be considered as multifactorial. (8) Although its etiology is clearly known and is related to the intake of immunosuppressive therapy in renal transplanted patients, different risks factors

associated with this condition have to be taken into account. They are classified as local and systemic factors. (17,23)

The most determinant are the drug variables, genetic predispositions and periodontal variables. (1,10)

Medically-induced gingival hyperplasia is related to the intake of systemic medication such as immunosuppressants, calcium channel blockers and anticonvulsants. (8) Several parameters such as the drug dosage, serum and salivary concentrations as well as the routes of administration need to be assessed as their imbalance can represent risk factors associated to drug-induced gingival hyperplasia in renal patients. Some studies have shown that these variables may influence some parameters such as the salivary secretion or plaque accumulation related to the routes of administration. Also, interactions with other drugs need to be taken into account in order to avoid side effects. (A.14) A correct equilibrium and control of the medication can reduce the risk to develop this condition or decrease its severity. (10,17)

Additionally, some evidences have shown that the age and the gender can influence the onset of the disease, as males are 3 times more affected than females and young people more susceptible to this condition. (8)

Bacterial plaque accumulation and irritative factors are considered as strong local risk factors associated to the etiology of gingival hyperplasia in renal patients. Indeed, Greenberg demonstrated statically that a significant correlation between plaque accumulation and gingival hyperplasia exists and can induce an inflammatory response increasing the onset and severity of the disease. (10,17,18)

In contrasts, other studies consider difficult to attribute a direct correlation between plaque accumulation and gingival hyperplasia. (21) they consider plaque accumulation as a contributive or aggravating factor, representing a consequence of pseudo-pockets related to the gingival alteration more than a primary effect resulting in the onset of gingival hyperplasia. (17) Several risk factors can be associated to medically-induced gingival hyperplasia in renal patient, but the medication parameters and the dental plaque seem to have a greatest impact on the risk to develop this condition. A good control of the risk factors will allow to prevent the onset or reduce the severity of medically-induced gingival hyperplasia in renal patients.

5.4 Dental management and treatment of gingival hyperplasia in renal patients

Drug-induced gingival hyperplasia is related to three categories of drugs, Immunosuppressors such as cyclosporin A, anticonvulsants such as phenytoin, and calcium channel blockers as Nifedipine and Amlodipine. Patients that undergo renal-transplant therapy are treated with immunosuppressive therapy to prevent the rejection of the graft as well as the reestablishment of the renal function but also calcium channel blockers to treat arterial hypertension. (22,23,24)

Cyclosporine-A is one of the most frequent Immunosuppressive medications used in renal transplanted patients. The dosage and control of this drug need to be assessed throughout renal patient's life as its intake can produce secondary effect such as gingival hyperplasia. (17) Thus, plaque control, elimination of plaque retentive factors, treatment of possible periodontal pathologies and periodic check-ups are essential for the prevention of this condition. (25)

It does not exist a specific therapeutic protocol for drug-induced gingival hyperplasia. The objective is the return to the physiological condition pleasing comfort and function and to answer an eventual esthetic demand. The possible treatment options can be classified as surgical and non-surgical therapies. (18)

Considering the patient’s benefit, stopping the causal medication and its substitution represent the first treatment option that should be considered. It requires an inter-consultation with the specialist in charge of the patient. Cyclosporin-A can be substituted by Tacrolimus, other possible immunosuppressive drug given to transplanted patients that has the same properties than Cyclosporin-A. After modification of the treatment, a partial reduction of the gingival hyperplasia can be observed between two and eight weeks. (8)

However, not all patients respond favorably to drug substitution. Related to the medication, The use of Azithromycin in renal patient’s management seems to have a significant positive effect on gingival growth indices and bleeding on probing, allowing the reduction of the gingival hyperplasia by its anti-proliferative and anti-inflammatory action. (21)

Plaque accumulation represents a contributive factor to drug-induced gingival hyperplasia. The non-surgical periodontal treatment is crucial in the management of renal patients affected by gingival hyperplasia. This treatment is based the mechanical elimination of tartar and subgingival microbiological biofilm and the decrease of the bacteriological load. It precedes all surgical treatments. (10). It includes oral hygiene control with tooth brushing, dental floss and interproximal toothbrushes, scaling and root planning, elimination of local irritative factors promoting plaque accumulation such as defective restorations, dental caries or broken tooth. (1) In some cases, an associated antibiotic prophylaxis with Amoxicillin and Clavulanic Acid 1g 2 times per day during 8 days can be given to decrease the bacteriological load. (10) A supportive treatment is than established based on the reinforcement of oral hygiene instructions and periodic dental check-ups every three months for the plaque control and the prevention of possible recurrence. (1) Non-surgical periodontal treatment allow to reduce the volume of gingival overgrowth of 40% or the complete elimination of it and the complete reattachment of the gingiva to the tooth producing the decrease of the periodontal pockets. On a histological point of view, we can observe the decrease of the inflammatory infiltrate and the production of fibroblasts. (10) With patient's cooperation, correct diagnosis and treatment planning, complex situations such as medically-induced gingival hyperplasia can be managed by simple non-surgical procedures.

When non-surgical periodontal treatments do not achieve the complete reduction of the gingival overgrowth, surgical procedures such as gingivectomy is indicated resulting in a smoother postoperative gingival surface. Both internal and external bevel incision can be performed depending on the extent of gingival hyperplasia and the height of the attached gingiva. (12) Theses procedures have higher risk of adverse effects than non-surgical procedures such as local bleeding, longer intervention, post-operative pain, cold and liquid diet in the following weeks and infectious complications. (18) The rate of recurrence is about 34% and can occur in the first 18 months after the surgery, due mainly to a non-effective plaque control and poor collaboration of the patient in regard to the periodic dental check-ups. (10)

Water laser therapy is also a therapeutic option to treat medically-induced gingival hyperplasia in renal patients as it compensates the disadvantages and adverse effects

of conventional gingivectomy. The most frequently used is the laser ER,Cr:YSGG, allowing to cut while protecting healthy tissues and eliminate tissue debris. It results into a better post-operative hemostasis, shorter intervention, requires less anesthesia and produce less post-operative discomfort. Laser therapy shows a great therapeutical effectiveness and a decrease in the recurrence rate compared to conventional surgery. However, it requires specific abilities form the clinician and is more expensive than conventional surgeries. (20)

Another non-conventional therapy for medically-induced gingival hyperplasia in renal patient is the photodynamic therapy. It consists in the application of a curcuma longa-based photosensitizer that has great affinity for the affected cells that absorb the light producing the selective elimination of them and the decrease of the inflammation and the bacterial load. Thanks to its anti-inflammatory, antiviral, antibacterial and anti-cancerous properties, it is applied directly inside the periodontal pockets to be activated by the light source. This procedure is painless and simple to realize, allowing an improvement of the depth of the periodontal pockets and a greater level of attachment. Other investigations need to be performed to evaluate the results of this technique. (18)

6 CONCLUSION

Chronic renal pathology is the result of a progressive loss of the renal function. Medically-induced gingival hyperplasia is one of the complications associated to the intake of immunosuppressive medication such as Cyclosporin-A, Tacrolimus and Nifedipine, that the renal transplanted patient needs to take throughout his life.

The exact histopathological mechanism of this condition is still unknown and more investigation need to be performed. However, studies show that it may be related to an increase of the collagenous and non-collagenous gingival cellular components, the fibroblasts proliferation and the decrease of their apoptosis but also an imbalance of the cytokines.

Clinical manifestations appear 1 to 3 months after starting the medication and most of the patients refer pain or discomfort, difficulties for plaque control and esthetic issues. In some cases, gingival hyperplasia can also affect the phonation and the mastication.

A precise intraoral and extraoral examination as well as a correct medical history and control of the risk factors are required for the evaluation, classification, diagnosis and management of medically-induced gingival hyperplasia in renal patient.

The goal of the treatment is to return to a physiological healthy gingival status, comfortable for the patient by the mean of surgical and non-surgical therapies. Rigorous plaque control and drug substitution in collaboration with the specialist will allow to reduce the inflammation and represent the first treatment options to consider. In case of persistence of the gingival hyperplasia, surgical procedures such as gingivectomy will be indicated. Other treatments such as laser or photodynamic therapy are used reducing the bleeding and promoting the healing of the gingiva, showing less post-operative disadvantages than surgical procedures. Regardless of the elected therapy, it is crucial to afford an appropriate supportive therapy to the patient insuring an effective plaque control and periodic dental check-ups every 3 months.

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