

# HUMAN PAPILLOMAVIRUS INFECTIONS AND RENAL TRANSPLANTATION: A REVIEW

## *INFECÇÕES CAUSADAS POR PAPILOMAVÍRUS HUMANOS E TRANSPLANTE RENAL: UMA REVISÃO*

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### ABSTRACT

The immune suppressive therapy in renal allograft recipients provides a favorable environment to the development of viral infections. Among them, human papillomavirus (HPV) infections are usually related to potential life-threatening mucocutaneous neoplasias. Data from clinical surveys suggest that transplant recipients may have up to 5-fold increased risk of developing multiple malignancies due to the increased susceptibility to persistent HPV infection. High risk HPV induced oncogenesis is a multi-step process in which a persistent infection is the initiating causative event, though subsequent genetic and epigenetic alterations may be necessary for malignant transformation. The main tumoral types associated with persistent HPV infection are anogenital, oral and skin cancers, common conditions in transplant recipients and responsible for substantial morbidity and mortality. Since prophylactic vaccines with high rates of efficacy have been approved for human population, studies to evaluate its immunogenicity and efficacy should be considered for long-term survivors after allogeneic transplantation. Hence, we conducted an extensive revision published data for the last 10 years regarding the theme. To achieve our objectives, we searched in diverse data basis such as Lilacs, SciELO, Medline, Scopus. We concluded that, concerning the increase in the population of transplant recipients as well as in the incidence of HPV associated diseases, measures for prevention and control are necessary, and include capacitating human resources and the use of last generation methodologies of diagnosis and prophylaxis.

**Keywords:** HPV, hyperplasia, neoplasia, cancer, renal transplantation

### RESUMO

A terapia imunossupressora em pacientes receptores de transplante renal fornece um ambiente favorável ao desenvolvimento de infecções virais. Dentre estas infecções, aquelas causadas pelos papilomavírus humanos (HPV) são geralmente associadas a neoplasias mucocutâneas que podem ameaçar a sobrevivência pós-transplante. Pesquisas clínicas sugerem que receptores de transplante podem apresentar um risco até cinco vezes maior de desenvolverem quadros de doenças malignas múltiplas, devido à maior frequência da persistência do HPV. A oncogênese induzida por HPV de alto risco é um processo de múltiplos estágios, no qual a infecção persistente é o evento fundamental, apesar de alterações genéticas e epigenéticas adicionais serem necessárias para a transformação maligna. Os principais tipos tumorais relacionados à infecção persistente por HPV são os cânceres anogenitais, orais e de pele, comuns em receptores de transplante e responsáveis por grande morbidade e mortalidade. Uma vez que vacinas profiláticas de alta eficácia contra a infecção pelo HPV foram aprovadas para uso na população humana, estudos para avaliar a imunogenicidade e eficácia destas vacinas em imunossuprimidos são recomendáveis. Assim, objetivamos fazer extensa revisão sobre o tema. Para tal, pesquisamos o assunto nas bases de dados Lilacs, SciELO, Medline, Scopus nos últimos 10 anos. Concluímos que, com o aumento na população de receptores de transplantes e a crescente incidência das doenças associadas ao HPV, medidas de prevenção e controle se fazem necessárias e englobam desde a formação de profissionais capacitados até a aplicação de metodologias de diagnóstico e profilaxia, de última geração.

**Palavras-chave:** HPV, hiperplasia, neoplasia, câncer, transplante renal

## INTRODUCTION

Solid organ transplantation is considered the best therapeutic approach for patients with end-stage organ failure. Liver, heart, lung and renal transplantation have become the standard therapy for some selected human diseases<sup>(1)</sup>. Prior to the advent of immunosuppressive therapy, kidney transplantation was limited to HLA-identical siblings and was not applicable to the vast majority of patients with terminal stage renal disease<sup>(2)</sup>. The advent of potent immunosuppressive therapy has improved graft outcome by facilitating grafting across histocompatibility boundaries. Nevertheless the advance in transplantation in the expense of impaired immune surveillance has led to long-term post transplantation complications, as seen for viral infections<sup>(3)</sup>.

Among the immune suppressors, the most commonly used are the calcineurin inhibitors (CI). The introduction of CI as an im-

munosuppressive drug in the early 80's was a striking event in the history of organ transplantation, decreasing the incidence of acute rejection episodes. At present, most immunosuppressive regimens combine a calcineurin inhibitor with an adjunctive agent (azathioprine, mycophenolate mofetil or sirolimus) and corticosteroids, resulting in a remarkable increase of patient survival. Currently, acute rejection occur in less than 10% of kidney transplant recipients, leading to excellent one-year graft survival<sup>(4)</sup>. The most used CsA is cyclosporine (cyclosporine A, CsA), being the main immunosuppressive drug for renal transplantation, followed by tacrolimus (FK-506).

Cyclosporin A is a hydrophobic cyclic endecapeptide with unsurpassed immunosuppressive activity. This drug binds to cyclophilin complex and inhibits calcineurin, a calcium and calmodulin-dependent serine threonine phosphatase responsible for the activation of nuclear factor of activated T cells. Cyclosporin inhibition of calcineurin leads to the inactivation of (NF-AT), consequently inhibition of interleukin-2 (IL-2), and preventing T cell activation. The pharmacodynamics of tacrolimus is very similar to CsA. It binds to FK-binding proteins; this complex inhibits calcineurin activity, thus inhibiting calcium dependent events. This leads to reduced IL-2 gene transcription, nitric oxide synthetase activation, cell degranulation and apoptosis. Tacrolimus is 100-fold more immunosu-

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pressive than CsA and is recognized as an effective alternative to CsA in primary and rescue therapies<sup>(5)</sup>.

Although the current immunosuppressive regimes have led to a decreased incidence of acute rejection, long-term immune suppressive therapy can induce a variety of side effects in transplant recipients. Calcineurin inhibitors themselves contribute to this problem through their nephrotoxic, cardiovascular and oncogenic side-effects, in addition to neurotoxicity and induction of diabetic state<sup>(4)</sup>. Thus, clinical focus has now shifted to the improvement of long-term outcomes and the development of different therapeutic strategies is highly necessary for this purpose.

The immunosuppressive therapy has provided a favorable environment to the development of infections which can be acquired in the community or from reactivated after transplant from both graft and host<sup>(6)</sup>. About 70% of all renal transplant recipients experience at least one infection episode by 3 years, accounting for 18% of all deaths with functioning grafts in the US<sup>(7)</sup>. Viral infections are severe complication of post-transplantation period, as they provoke hard management diseases, favor graft injury or loss, and cause fatalities<sup>(3,6)</sup>.

Cytomegalovirus remains the most prominent virus in transplantation. Nevertheless, several emerging viral pathogens have been described recently in transplant recipients<sup>(8)</sup>. Human papillomavirus (HPV) infections cause potentially life-threatening cutaneous and anogenital neoplasias. The overall pattern of data from clinical surveys suggests that some transplant recipients may also have an increased susceptibility to HPV persistent infection, with a 5-fold increased risk of developing multiple malignancies<sup>(9,10)</sup>. In this review, we aim to discuss the most common forms of lesions associated to HPV infection in kidney transplant recipients.

## Human papillomavirus: basic virology, pathogenesis and immunology

Human papillomavirus (HPV) are small DNA viruses classified in the *Papillomaviridae* family. More than 100 types of HPV have been recognized on the basis of DNA sequence data. The viral particle is surrounded by a non-enveloped icosahedral capsid measuring 55nm, composed of two structural proteins: the L1 which comprises 80% of the total viral proteins and the L2, a minor capsid component. The viral genome is a double-stranded circular DNA of approximately 7.9 kb in length, encoding the open reading frames (ORFs) classified as early (E) or late (L), depending on the time point of gene transcription<sup>(11,12)</sup>.

HPV can infect basal epithelial cells of skin or mucosal tissues. They are associated to the development of skin and genital warts and have been well-established as the sexually transmitted agent of cervical cancer and its precancerous associated lesions<sup>(12,13)</sup>. Based on their association with cervical cancer and precursor lesions, HPV can also be grouped as high-risk (HR-HPV) and low-risk (LR-HPV) types. The low-risk types include HPV 6, 11, 42, 43, and 44, while high risk types include HPV 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70<sup>(14,15)</sup>.

HR-HPV-induced carcinogenesis is a multi-step process in which a persistent infection is the initiating causative event, but subsequent genetic and epigenetic alterations are necessary for an infected cell to become fully malignant<sup>(15-17)</sup>. HR-HPV exert their

oncogenic effect by expressing the oncoproteins E6 and E7, which bind to and inactivate the p53 and Rb tumor suppressor gene products, respectively<sup>(18)</sup>. These genes can transform human cells and the inhibition of their expression in cancer cells result in loss of neoplastic growth properties<sup>(17)</sup>. Furthermore, oncogenic HPV types interfere with control of the cell division cycle and apoptosis through the disturbance of the cyclin-dependent kinases (CDKs) pathways, important cell cycle inducers. Their inhibitory proteins (CDKIs) block specific interactions, leading to cell cycle arrest. The Ink4 (inhibitor of cdk4) class of cdkis (p16<sup>Ink4a</sup>, p15<sup>Ink4b</sup>, p18<sup>Ink4c</sup>, and p19<sup>Ink4</sup>) bind and inhibit cyclin D-associated kinases (cdk2, -4, and -6), therefore blocking their activity. p16 is a tumor suppressor protein belonging to the family of INK4 cyclin-dependent-kinase inhibitors whose increased expression has been associated with HPV-infected dysplastic and neoplastic epithelium of the cervix<sup>(19)</sup>. The functional inactivation of pRb by HR-HPV E7 results in the reciprocal over expression of p16<sup>INK4a</sup>, due to a negative feedback loop between pRb and p16<sup>INK4a</sup>.

Therefore, over expression of p16<sup>INK4a</sup> may be used as a marker of viral involvement<sup>(17-19)</sup>. HPV infects basal keratinocytes probably via microabrasions of the epithelial surface. Although the precise entry mechanisms remain unclear, it is believed that HPV attachment is mediated by heparin-sulfate proteoglycans. Apparently, viral entry occurs through endocytosis via clathrins that guide HPV particles into caveosomes, and posterior pH decrease leads to DNA release. Viral genome is then transported to the nucleus and remains as episomal DNA. The viral proteins production is initiated at defined periods, through tight regulation of viral gene expression while the infected cell migrates towards the epithelial surface<sup>(20)</sup>.

All events in the viral life cycle are strictly linked to the differentiation program of the keratinocyte. Since HPV is not a lytic virus and the terminal events that result in genome encapsidation, assembly and maturation of infectious virus occur in the most superficial differentiated cells of squamous epithelium, no inflammation accompanies viral infection due to a lack of danger signals to alert the innate immune sensors<sup>(21)</sup>.

HPV have several mechanisms of immune escape. During replication, viral antigens are not presented via MHC-I until the infected cells are differentiated. The epithelial differentiation process occurs in the superficial layers, where dendritic cells can no longer reach. Besides, studies have pointed out that HPV E6 and E7 proteins promote a negative regulation of functions related the signaling of cytokines such as interferon (IFN). HPV-infected cells are also resistant to natural cell killer (NK) cells, but can be destroyed by NK cells activated by cytokines and macrophages. Despite the difficulties that HPV natural infection brings to immune surveillance, the histological examination of regressing warts reveals large infiltrate of T cells (CD4+ and CD8+) in epithelium and stroma. These lymphocytes actively express pro-inflammatory cytokines, triggering a Th1 response. Thus, the immunity against HPV is essential for its clearance and the lack of such response may lead to increased risk of persistent infections<sup>(21)</sup>.

The incidence of virus-related malignancies is increasing among immunosuppressed populations, such as transplant recipients receiving immunosuppressive therapy, suggesting that immunodeficiency is risk factor for malignancy. As the life expectancy for chronically immunosuppressed patients continues to

rise, malignancy will likely become an increasing complication for these patients<sup>(22)</sup>.

Anogenital, oral, pharyngeal and skin cancers are common malignant conditions in transplant recipients and account for substantial morbidity and mortality in such patients. Among immunosuppressed patients, the risk for developing SCC is 10 to 250-fold increased in comparison to immunocompetent individuals<sup>(23)</sup>. HR-HPV persistent infection mainly caused by types 16 and 18, have been implicated in the etiology of SCC of the female genital tract, head and neck<sup>(20)</sup>. Significantly higher levels of HPV DNA have been reported in SCC from immunocompromised versus immunocompetent patients, possibly because of higher HPV viral loads in the former.

HPV coinfections with other viral agents in skin and mucous tissues have also been reported in immunosuppressed individuals. Herpesvirus such as EBV; CMV; HSV 1 and 2; HHV 6 and 7 and Merkel Cell Polyomavirus have been encountered in HPV-positive lesions but their role in the pathogenesis of HPV infection remains obscure<sup>(8)</sup>. Although these are classic opportunistic agents, it is not clear whether viral infection or immuno-mediated suppression, or maybe both, creates a permissive environment for HPV replication or vice-versa (unpublished data).

### Oral lesions associated to renal transplantation

In transplant recipients, immunosuppressive drugs, severely disrupt immune function and can also have direct effects at the site of tumor formation<sup>(24,25)</sup>. Acting along with possible viral infection such as HPV, these changes create a setting in which cell transformation is enhanced and tumor cells can gain advantage. In this scenario, those tumors linked to oncogenic viruses are potentially more immunogenic through presentation of viral peptides than tumors arising from chemical or environmental carcinogenesis, which may not be readily recognized as non-self. Because of this, growth of virus-associated tumors may be more amenable to reversal by the host immune system when immunosuppression is reduced<sup>(26)</sup>.

A general propensity for oral epithelial neoplasia is apparent in immune-suppressed allograft recipients. Bustos et al.<sup>(27)</sup> detected HPV in oral lesions from kidney transplant patients. HPV DNA has been detected in up to 70% of the malignant tissues and HPV 16 was the predominant type. Rose et al.<sup>(28)</sup>, investigating asymptomatic HPV infection in oral cavity, showed HPV DNA in 18% of renal transplant versus 1% of control samples. Prospective molecular-epidemiological studies are still necessary to confirm the potential role of HPV in malignant transformation of oral cavity in immune-suppressed individuals.

Atypical pathologies have also been described in these patients, being gingival overgrowth (GO) one the most relevant. Al-Osman et al.<sup>(29)</sup> reported a case of extensive GO lesions in a renal transplant recipient, associated with HPV-16 infection.

GO secondary to the administration of CsA was firstly described by Calne et al.<sup>(30)</sup> and is a very common reported side-effect of chronic renal disease on periodontal tissues. Despite being a benign condition, it can compromise life quality. Its histopathologic features resemble the benign hyperplasia caused by human papillomavirus infections. Nevertheless it is still an idiopathic condition that deserves further studies.

GO begins with papillary enlargement, more evident on the labial gingival face rather than the palatal or lingual surface. This is characterized by an accumulation of extracellular matrix within the gingival connective tissue, particularly the collagenous component, with various degrees of chronic inflammation. The disfiguring aspect of GO may interfere with normal oral functions and cause impaired speech, headache and difficulty in maintaining optimal oral hygiene resulting in an increased susceptibility to infections, dental cavities and periodontal diseases. Besides, it may have a psychological impact and in turn influence compliance with medical therapy<sup>(31)</sup>.

There is a wide intra and inter-individual variability in the susceptibility of the cyclosporine to induced GO and recent studies show that the prevalence among renal transplant patients under CsA immunosuppressive therapy varies from 8 to 70%<sup>(31,32)</sup>. Although of high importance, gingival overgrowth pathogenesis has not yet been elucidated and is considered a multi-factor process.

### Skin lesions associated to renal transplantation

The earliest evidence for the involvement of specific HPV types in human skin cancer were originated from observations of patients suffering from a hereditary disorder, known as epidermodysplasia verruciformis (EV). About one-third of the EV patients develop multifocal cutaneous squamous cell carcinomas, mainly on sun-exposed parts of the body. These patients are commonly infected with a group of genotypic-related HPV that induce disseminated macular skin lesions over the body<sup>(33)</sup>.

Most studies examining the involvement of papillomaviruses in the development of cutaneous carcinomas have been done on lesions that have developed in patients with the hereditary EV or subjected to prolonged periods of immune-suppression such as renal allograft recipients. Both types of patients develop extensive cutaneous papillomatous lesions which initially appear as benign keratosis and frequently progress to dysplasia and carcinoma *in situ* (CIS) or invasive carcinoma on sun-exposed sites<sup>(34)</sup>.

It has been reported that skin cancer is the most commonly encountered malignancy in renal transplant recipients, with 37.4–63% of all post-transplantation tumors<sup>(35,36)</sup>. After the statement of a possible role of HPV as the etiological agent of many skin lesions, several studies have pointed out the importance of this infection in kidney recipients. Suppression of cellular immune responses is undoubtedly an important factor, but infection with human papillomaviruses may also be involved in skin carcinogenesis<sup>(37)</sup>.

Clinical and histological analysis showed the progression of viral warts to dysplastic lesions and invasive squamous cell carcinomas in immunosuppressed patients<sup>(38)</sup>. Thus, viral warts that are usually considered benign in immunocompetent patients may have a different prognostic in immune-suppressed patients. Studies have reported a risk of 14% of neoplasia development in the first 10 years after transplantation, increasing to 40% after 20 years<sup>(39)</sup>.

Most of the information regarding skin cancer is from the era of cyclosporine and whether the new transplantation immunosuppressive medications will alter the behavior of skin cancer in organ transplant recipients remains to be determined. Immunosuppressive therapy also increases the rate of non-malignant and malignant skin lesions in kidney recipients<sup>(40)</sup>. Thus, any skin infectious

lesions should be carefully considered, in order to reduce the risk of transformation into malignancy. It seems that early diagnosis and treatment of human papillomavirus infection in immunosuppressed patients would prevent development of lesions related to poor prognosis.

### Cervical lesions associated to renal transplantation

According to Savani et al.<sup>(37)</sup>, the risk for squamous cell carcinomas (SCCs) was five-fold higher in patients with a history of chronic graft versus host disease (cGVHD) in comparison to general population. In regard to female genital tract, Meeuwis et al.<sup>(24)</sup> reported a six-fold risk to develop cervical intraepithelial neoplasia, three-fold for cervical carcinoma and 50-fold for vulvar carcinoma. HPV is the necessary cause of cervical cancer and HPV-16 is the most prevalent type seen in cervical SCC worldwide<sup>(41)</sup>.

Recent studies have demonstrated a higher susceptibility of transplanted patients to HPV cervical infection<sup>(41,42)</sup>. Besides that, it is known that neoplastic lesions show high aggressive profile associated with a frequent multi-focality<sup>(43)</sup>.

Cervical SCC is a frequent solid tumor in long-term stem cell transplant (SCT) survivors. A 13-fold increased risk compared to the general population has been reported<sup>(44)</sup>. Savani et al.<sup>(37)</sup> reported a higher prevalence of cervical dysplasia in long-term survivors after allo-SCT, occurring in more than one third of patients. Lower genital tract dysplasia is also common among solid organ transplant recipients<sup>(45)</sup>. The reported prevalence of genital HPV in the general population ranges from 20% to 46%<sup>(46-48)</sup>, but can be as high as 64% after allogeneic transplantation<sup>(49)</sup>.

Although HPV infection is common, studies suggest that 90% of infections clear within 2 years<sup>(50)</sup>. HPV may reactivate and lead to SCC in long-term SCT survivors. Savani et al.<sup>(37)</sup> found increased prevalence of cervical dysplasia in non-sexually active long-term survivors, suggesting that HPV reactivated.

It is important to notice that other HPV-related cancers such as vaginal/vulvar and penile cancers have also presented increased incidence in long-term survivors. Guidelines for the screening and prevention of second malignancies would be helpful in reducing the risk of cancer development.

### Anal lesions associated to renal transplantation

HPV has been implicated as a significant factor in anal carcinogenesis. Eighty-four percent of anal cancers are associated with oncogenic/high-risk HPV, being type 16 as the most prevalent, accounting for 70% of anal carcinomas<sup>(51)</sup>. Anal carcinoma was a relatively uncommon malignancy with an incidence of 0.7/100,000 men and 0.9/100,000 women.

The incidence of high-grade dysplasia and cancers of the anogenital region is estimated to be 10 to 100-fold higher in transplant recipients than in the general population, with women twice as affected as men<sup>(52,53)</sup>. In a recent review, Hinten and cols described a 100-fold risk of developing anal lesion in women<sup>(54)</sup>. Patients who receive allografts during childhood are also at increased risk of anogenital cancer, with a mean interval of 7 years between transplantation and diagnosis<sup>(42)</sup>. It is widely believed that the excess cancer risk following organ transplantation is related to the

necessary immune modulation, but there is emerging evidence that newer immunosuppressive drugs may confer a lower risk<sup>(55,56)</sup>.

### Prevention and control

Since prophylactic vaccines have been approved for human population, showing high rates of efficacy, studies to evaluate the immunogenicity and efficacy of HPV vaccine should be considered for both male and female long-term survivors after allogeneic transplantation, in order to prevent lesions that are extremely difficult to treat, as suggested by Tedeschi et al.<sup>(22)</sup>.

### CONCLUSION

After conducting an extensive revision, searching in diverse data basis such as Lilacs, ScIELO, Medline, Scopus, we concluded that, concerning the increase in the population of transplant recipients and in the incidence of HPV associated diseases, measures for prevention and control are necessary, and include capacitating human resources as well as the use of last generation methodologies of diagnosis and prophylaxis.

### Conflict of interest

The Authors declare that there is no conflict of interest.

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