CLINICAL STUDIES ON GENITAL PSORIASIS AND HPV-RELATED LESIONS

A MULTIDISCIPLINARY APPROACH

KIM A.P. MEEUWIS

Clinical studies on genital psoriasis and HPV-related lesions

a multidisciplinary approach

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1.1 Anogenital skin

The anogenital area forms a unique environment comprising the external genitalia, perineum and anus and is covered with different types of epithelium. The external genitalia consist of the vulva of females and the penis and scrotum of males.

The vulva is the generic term for all structures of the female external genital tract and includes the mons pubis, paired labia majora and minora, clitoris, the vestibule of the vagina and the urethral orifice. The hymen partially conceals the vaginal opening and forms the separation between vulva and vagina. The vulvar epithelium changes from stratified, keratinised squamous cell epithelium on the outer parts to mucosa on the innermost regions. The 'line of Hart', at the inside of the labia minora reflects the sharp demarcation between keratinised and non-keratinised squamous cell epithelium.[1,2]

The male external genitalia include the penile shaft, glans, prepuce and scrotum. The prepuce forms the anatomical covering of the glans penis and is the junction between the mucosal surface of the glans and coronal sulcus and the keratinised squamous cell epithelium of the remaining external genital skin.[3] The perineum connects the external genitalia to the perianal region; both are covered with keratinised skin. The external perianal skin is continuous with the skin of the anal opening and the keratinised layer of the internal wall of the anal canal.

The skin functions as an important barrier to protect individuals from damaging external influences. This is particularly beneficial in the anogenital area because of exposure to a wide range of micro-organisms, mechanical and chemical irritants. Due to the combination of moisture, warmth and friction, anogenital skin folds are susceptible to maceration and fissuring.

The normal characteristics of common dermatoses may be lost or modified in the genital region and these dermatoses may be confused with sexually transmitted diseases. Anogenital dermatoses are associated with considerable morbidity, discomfort and embarrassment and may considerably impair quality of life and psychosexual wellbeing of patients. Because of the high sensitivity of the vulnerable thin genital skin and the increased penetration of topical treatments applied to this site of the body, treatment of genital lesions is a challenge.

1.2 Genital psoriasis

1.2.1 Epidemiology

Psoriasis is a multi-factorial, chronic, immune-mediated hyperproliferative inflammatory skin disease with a high prevalence in the general population of about 2%.[4-6] It is one of the most commonly seen dermatoses at genital skin, although often limited

attention is paid to the genital presentation of this skin disease. Remarkably few data exist on the involvement of the genitalia in patients with psoriasis and moreover, the anogenital region is frequently overlooked in daily clinical care for these patients.

In many cases, genital psoriasis is part of more generalised plaque psoriasis, although the external genitalia may be the only area affected. However, the isolated presentation of psoriasis solely on genital skin seems to be rare and occurs in only 2-5% of the psoriatic patients. Psoriasis on genital skin also occurs in cases of intertriginous (synonym: flexural) psoriasis.[2,6-8] In both literature and daily clinical practice, genital psoriasis is often classified as intertriginous psoriasis.

Several questionnaire-based surveys show that involvement of the genitalia occurs in 29-40% of patients with psoriasis. Male patients seem to suffer more frequently from genital psoriasis compared to female patients.[9-13] Overall, about 2-4% of patients referred to specialised clinics with genital dermatoses are diagnosed with psoriasis.[14-18]

Prevalence rates of genital psoriasis in children are scarce. However, two studies indicate that vulvar psoriasis is one of the most common diagnoses in prepubertal girls with vulvar complaints (affecting 10-17% of the patients).[17,19]

1.2.2 Clinical presentation

Psoriatic lesions on genital skin often present as well-demarcated, brightly erythematous, thin plaques.[20-38] When scaling is present, it is often minimal and can easily be scraped off, leaving pinpoint bleedings.[25,26,37,39]

Vulvar psoriasis is often symmetrical and can vary from silvery scaling patches adjacent to the outer parts of the labia majora to moist greyish plaques or glossy red plaques without scaling in the skin folds.[32,34,39-43]

In male patients, the glans penis is the area that is most commonly affected with psoriasis. Occasionally, the entire penis, scrotum, and inguinal folds are involved.[24,25,29,44,45] In uncircumcised males most commonly well-defined non-scaling plaques are present under the prepuce and on the proximal glans. In circumcised patients, usually erythematous lesions that may be scaly are present on the glans and corona.[24,29,44]

Genital lesions may be accompanied by rhagades or fissures, which can cause definite soreness.[27,46] Patients with genital psoriasis may also experience pruritus and/or a burning sensation in the affected area.[22,25,29,35,39,47] Although most genital psoriatic lesions represent plaque-type psoriasis, the genital area may incidentally also be affected by generalised or localised pustular psoriasis.[48-50] Due to the Koebner phenomenon, genital psoriasis may be worsened by irritation from urine and faeces, tight-fitting clothes and sexual intercourse.[25,37,41,51]

There is no difference in the clinical presentation of genital psoriasis between children and adults, although it has been debated whether a psoriatic diaper eruption should be regarded as psoriasis, seborrhoic dermatitis or a Candida infection. It is

currently assumed that both localised and disseminated psoriatic diaper eruptions may represent psoriasis or a precursor to psoriasis in some children.[36,52-56]

1.2.3 Diagnosis

The diagnosis of genital psoriasis can usually be made on the basis of its clinical appearance. Genital psoriatic lesions often are part of a more generalised form of psoriasis and confirmatory lesions elsewhere or other clinical signs of psoriasis (such as nail deformities or joint complaints) may be present.[19,21-24,26,27,29,30,32,34,35,39,40,43-45] Skin biopsies are therefore rarely needed, but should not be omitted in inconclusive cases. Possible differential diagnoses for genital psoriasis are shown in Table 1.

Table 1 Possible differential diagnoses for genital psoriasis as mentioned in referred articles

Differential diagnose	References
Dermatitis (variants: seborrhoic dermatitis, contact dermatitis, atopic dermatitis, spongiotic dermatitis)	15,21,22,33,34,39,43,49,53,62
Tinea or candidiasis	15,21,33,39,41,51,62
Squamous cell carcinoma (in situ) (variants: morbus Bowen, Bowenoid papulosis, erythroplasia de Queyrat)	20,25,29,33,44,45,49
Plasma-cell balanitis or vulvitis	20,33,41,44,45,49
Lichen planus	21,39,44,45,49
Secondary or tertiary (pustular) syphilis	21,39,45,49,50
Reiter's syndrome (balanitis circinata)	44,49-51
Lichen simplex chronicus (excoriated)	15,22,39
Extramammary Paget's disease	20,39
Intertrigo	21,33
Fixed drug eruption	44,49
Lichen nitidus	49
Lichen sclerosus	22
Scabies or pediculosis pubis	39

The main histopathological features of psoriasis are: 1) epidermal hyperplasia with regular elongated rete ridges 2) marked hyperkeratosis, mainly composed of parakeratosis 3) prominent dilated and elongated superficial capillaries in the dermis and 4) dermal inflammatory lymphocytic infiltrate. There is no apparent histological

difference between genital and non-genital psoriasis. [14,15,21,22,26,27,33,44,57]. However, the typical histopathological features of psoriasis might be less evident in genital lesions, because of the thin keratinised layer and less evident epithelial hyperplasia.[57,58]

1.2.4 Therapy

Numerous different treatment options are available for psoriasis. A division into three main modalities, including topical treatment, photo(chemo)therapy and systemic treatment can be made. The current literature (predominantly reflecting expert opinions and a few case reports) provides extremely limited evidence for the efficacy and safety of treatment options for genital psoriasis.

Corticosteroids

Topical corticosteroids are the mainstay in genital psoriasis therapy. The many available formulations are classified into four potency groups, based on their clinical effectiveness: I weak, II moderate, III potent, IV ultra-potent.

The current literature reflects a reluctance in the prescription of (ultra-)potent corticosteroids for genital psoriasis and generally recommends the use of weak (and sometimes, if necessary, moderate) corticosteroids, which may be combined with vitamin D analogues or coal tar preparations.[24,25,31-33,41,44,51,59,60] However, although weak corticosteroids are preferable because of their mild side effects, they often seem insufficiently potent to induce a response. Therefore, short term, intermittent use of moderately potent corticosteroids to induce a response, followed by a subsequent gradual shift towards a weak steroid preparation is sometimes advised.[14,34,35,40,42,43,61] On the contrary, intensive, short-term, intermittent use of potent corticosteroids is also occasionally advised.[21,22,28,29,45,62,63] The application of corticosteroids in the genital region may induce symptomatic candidiasis.

Coal tar preparations

Coal tar preparations have been used in the treatment of various skin diseases for a long time. The preparations mainly used in dermatological practice are crude coal tar (pix lithantracis) and its extract liquor carbonis detergens.

Coal tar preparations are the second-most advised topical therapy for the treatment of genital psoriasis. Mild topical coal tar preparations (i.e. 1-5% liquor carbonis detergens in aqueous cream) are advised frequently. They may be used as an individual topical therapy or, when (maintenance) treatment with weak corticosteroids is insufficient, be combined or alternated with topical corticosteroids.[24,34,35,41-44,61] Coal tar may also be used for diaper psoriasis, for example mixed with zinc oxide.[59,60] These preparations are generally well tolerated in the anogenital region, however irritation and folliculitis can occur.[21,28,31,32,41] Other disadvantages of coal tar preparations are its staining and odour.

Vitamin D analogues

Vitamin D analogues are valuable in the treatment of genital psoriasis, because of their corticosteroid sparing ability and long-term safety profile.[24,25,29,45] They can be prescribed as monotherapy or in combination with corticosteroids.[24] Irritation and burning at the applied area are known side effects of vitamin D analogues, particularly at the genital skin. These side effects may be minimised by a combination with corticosteroids.[24,45] Sometimes however, vitamin D analogues remain too irritating to apply to the genital area.[32,60]

Calcineurin inhibitors

Topical calcineurin inhibitors (pimecrolimus ointment or tacrolimus cream) are often used in the treatment of facial and intertriginous psoriasis. The current literature provides only very weak evidence for the use of these immune-modulating preparations for the treatment of genital psoriasis.[32] Topical calcineurin inhibitors may cause local irritation and stinging after application. Monitoring of possible complications of calcineurin inhibitors is advised, as they can cause irritant or allergic contact dermatitis, candidiasis, or (re)activation of viral skin infections. The risk of carcinogenicity from topical immunomodulators is unknown up until now. A careful risk-benefit assessment is therefore advised before topical calcineurin inhibitors are prescribed.[64]

Other modalities/general advices

Emollients moisturise, soften and protect the skin. They may reduce redness, itch and pain caused by psoriatic lesions and belong to the basic genital psoriasis therapy. Besides, minimising the contact with local irritating factors is useful in the treatment of genital psoriasis.[28,41,45,62]

Suspected concurrent bacterial or fungal infections of the genital area should be treated with topical antibiotics or antimycotics, respectively, to eliminate the possible Koebner effect.[22,25,29,31,34,35,41,45,60]

Dithranol (anthralin), topical retinoids/retinoid analogues and photo(chemo) therapy (psoralen plus ultraviolet A (PUVA), ultraviolet B (UVB) and laser) should be avoided in the genital area, because of their high irritating potential.[21,32,41] Besides, both PUVA and UVB phototherapy, carry an increased risk of developing genital squamous cell carcinoma (SCC), particularly in men.[65,66]

Systemic therapy is no common practice for isolated genital psoriasis. Nevertheless, such treatment modalities may also be beneficial for genital lesions if prescribed because of severe and extensive psoriasis.[31,32]

Therapy-resistant penile and vulvar plaques should always be clinically and histologically re-evaluated to rule out any (pre-)malignancy.[25,29,39] The choice of treatment should always be individualised for each patient. Besides the given

therapeutic arsenal, education and psychological/sexuological support is of extreme value in the care for patients with genital psoriasis.

1.3 HPV-related genital (pre)malignancies in female renal transplant recipients

1.3.1 Renal transplantation, immunosuppressive therapy and post-transplant malignancies

The first renal transplantation (RT) was performed between identical twins in 1954. Five years later, a succesful RT was made between non-identical twins. Following this, promising attempts to transplant other organs were made. At present, solid organ transplantations are performed routinely in many countries: about 18.000 RTs are performed each year in the European Union (500 million inhabitants).[67] After solid organ transplantation, the administration of lifelong intense immunosuppressive therapy is required.

Immunosuppressive therapy has developed over the years towards combination therapy with several immunosuppressive drugs. The current 1-year patient and renal transplant survival exceeds 90%.[68] Initially, the clinical management of organ transplant recipients was dominated by acute post-operative problems, acute rejection, infection and cardiovascular disease. However, the improvement of immunosuppressive protocols and anti-infectious therapy has led to a decrease of these problems.[69,70]

As a consequence of the improved long term survival of renal transplant recipients (RTRs), there is a tremendous increase in the incidence of post-transplant malignancies. It is known that the overall incidence rate of cancer in RTRs is at least three- to fivefold increased compared to the general population with similar age and gender distribution.[71-74] However, the elevated risk for specific cancers, such as non-melanoma skin cancer (NMSC), cancer of the lip, Kaposi sarcoma, post-transplant lymphoproliferative disease (PTLD) and Human papillomavirus (HPV) related anogenital malignancies is known to be even higher.[71-77] Besides NMSC, which is extremely common in RTRs, the cumulative risk to develop any malignancy has been estimated at 20% after 10 years of chronic immunosuppression. Over the next 20 years, mortality from cancer may exceed that from cardiovascular disease among transplant recipients.[70]

The aetiology of post-transplant malignancies is multifactorial, with a main role for the use of immunosuppressive medication. The duration and dose of immunosuppressants is clearly linked to the appearance of post-transplant cancer.[70,78,79] Various immunosuppressants (e.g. azathioprine and cyclosporine) may have direct carcinogenic effects by inhibiting DNA repair capacity or by the production of

growth factors, which may lead to irreversible DNA alteration and subsequent carcinogenesis.[72,80-83]

In addition, immunosuppressive agents may indirectly contribute to the development of cancer, as an impaired surveillance ability of T-cells may disrupt anti-tumour immune surveillance and may potentiate oncogenic stimuli as chemical carcinogens, ultraviolet (UV) light and viruses.[70,84,85] Viruses that are associated with the development of cancer in RTRs are the Epstein-Barr virus which can induce PTLD and the hepatitis B/C viruses which are linked to the development of hepatocellular carcinoma.[86-91] Besides, various subtypes of HPV are associated with SCC of the cervix, vulva, perineum and anus.[84,92] It is also suggested that HPV infection may act as cofactor with UV-radiation in the carcinogenesis of extragenital NMSC. However, whether HPV plays a causal role in the oncogenesis of NMSC remains a matter of debate.[93-98]

1.3.2 Human papillomavirus

The human papillomavirus is a double stranded circular DNA virus that belongs to the Papillomaviridae family. To date, more than 150 HPV genotypes have been completely sequenced.[99] The virusses have co-evolved with their hosts over millions of years and many HPV genotypes cause only inapparent, asymptomatic infections in immunocompetent individuals. Papillomavirus types found in humans are divided into five genera based on DNA sequence analysis, with the different types having different life-cycle characteristics and disease associations. Based on their tissue preferences, HPV can be divided in cutaneous and mucosal genotypes.

Cutaneous HPV genotypes (most of which are in the Beta and Gamma genera) are found in the skin and cause cutaneous verruccae.[94,99] Cutaneous genotypes are generally not associated with the development of cancer, although certain types have been implicated in the development of NMSC in immunocompromised individuals and in epidermodysplasia verruciformis patients.[94,99]

Mucosal HPV genotypes (within the Alpha genera) are found in mucosal epithelium of the oropharynx and anogenital tract. According to their carcinogenicity, mucosal HPV is further subdivided into low-risk mucosal types (causing condylomata acuminata; mainly genotype 6 and 11) and high-risk types (causing anogenital neoplasia and cancer; mainly genotype 16 and 18).[99-101]

Acquisition of genital HPV is very common and is mainly transmitted by sexual intercourse.[102] The overall worldwide HPV prevalence is approximately 10%, with higher proportions in the young age groups.[103-105] The lifetime risk for infection with one or more HPV subtypes is up to 80%.[99,103,106,107] However, the majority of these infections is transient and will be cleared by the immunesystem without causing any lesions. Only when HPV infections persist long enough, neoplasia and subsequent cancer will arise.

The natural host tissue of HPV is the differentiating epithelial layer of skin or mucosa. The life cycle of the virus is initiated when it infects basal epithelial cells, after which the virus replicates and produces viral particles during epithelial differentiation. The HPV genome encodes for 9 viral proteins; the specific early ('E')-region encodes for regulatory, transforming and replication viral proteins which are expressed in un- to moderately differentiated basal replicating cells. The late ('L')-region encodes for viral capside proteins which are only expressed in highly differentiated epithelial cells, resulting in a high number of HPV copies in superficial epithelial layers (see Figure 1).[108]

A persistent infection with high-risk HPV (hrHPV) may lead to integration of the viral DNA into the human genome. Integration is characterised by deletion of the viral E2 region, that leads to an over expression of the viral E6 and E7 oncoproteins. These proteins are known cancer promoting genes that may inactivate the key cellular proteins p53 and retinoblastoma protein which leads to chromosomal instability, diminished apoptosis and enhanced cell proliferation. [102,109]

1.3.3 Cervical (pre)malignancies

Cervical cancer is a major health problem, with more than 500.000 new cases occurring each year worldwide, especially in developing countries. Yearly about 250.000 deaths from cervical cancer are reported, making it the third leading cause of cancer death in women in the world.[109] In developed countries, cervical cancer has been considered a preventable cancer because of its long pre-invasive state, cervical screening cytology programmes to detect pre-invasive lesions at an early stage and the possibility to treat these premalignancies. Virtually all cervical cancers are caused by hrHPV infection, which implies that cervical cancer does not and will not develop in the absence of the persistent presence of HPV.[110] HPV 16 accounts for 50 – 60% of the cervical cancer cases in most countries, followed by HPV 18 (10 – 20%).[105,110,111]

The primary site for cervical cancer is the cervical transformation zone (border between the glandular and squamous epithelium). The transformation zone is assumed to be more susceptible to oncogenic influences, like hrHPV infection, due to the high cell-turnover.[112] Virtually all cases of cervical cancer develop through the following distinct and sequential steps: acute infection with hrHPV followed by detectable viral persistence linked to the development of cervical intraepithelial neoplasia (CIN) and subsequent invasion.[113] About ten percent of the hrHPV infections that persist for several years is linked to the development of CIN.[114] CIN lesions are classified as CIN 1, CIN 2 and CIN 3 on the basis of the presence of mitotic activity and nuclear atypia within respectively the basal third, two thirds and whole thickness of the epithelium.[115]

In general, the prognosis of cervical cancer is good with an overall 5-year survival of 65% and for stage I disease a 5-year survival up to 98%.[116] On the other hand, the

morbidity after treatment is impressive with infertility, ovarian dysfunction, micturition/ defecation problems and sexual discomfort as the most imposing complications.[117]

1.3.4 Vulvar (pre)malignancies

Vulvar cancer is a rare disease which accounts for approximately 3-5% of all gynaecological cancers, with an incidence of about 2 per 100.000 women.[118,119] In the Netherlands, about 300 new cases of vulvar SCC are diagnosed per year.[118,119] There has long been a three-grade system to define vulvar SCC precursors (vulvar intraepithelial neoplasia [VIN] grade 1-3), analogous with CIN lesions. However, as clinicopathological data did not support the concept of a continuous spectrum of VIN lesions leading to vulvar cancer, the International Society for the Study of Vulvovaginal Disease (ISSVD) modified the classification of VIN. VIN 1 was abandoned and VIN 2 and 3 were consolidated into one category simply termed VIN. Subsequently, as the single diagnostic category VIN included two different vulvar premalignancies that have a different malignant potential, the classification was modified into VIN differentiated type (dVIN) and VIN usual type (uVIN).[120]

Vulvar SCC originates from two separate pathways. The first is an HPV-independent pathway and occurs in a background of non-neoplastic epithelial disorders (e.g. lichen sclerosus). This form is usually seen in older women and encompasses the majority of vulvar SCCs in the general population (about 80%).[121,122] Differentiated VIN is presumed to be the precursor lesion of the HPV-negative vulvar SCC.[118,123]

The second pathway is an HPV-dependent pathway, caused by a persistent infection with hrHPV. HrHPV subtypes 16 and 33 are the most commonly seen genotypes in vulvar lesions, present in about 60% and 20% of HPV-dependent vulvar carcinomas in the general population respectively.[121,124-126] The premalignant stage for this tumour is uVIN.[121,127] The oncogenesis of this type of vulvar SCC has a remarkable resemblance to the development of CIN into cervical cancer. The immune system seems to play an important role in the progression of uVIN to invasive disease.[128] HPV-dependent vulvar SCCs primarily affect younger women and comprehend the minority of vulvar malignancies in the general population (about 20%).[121,126] Oppositely, HPV-dependent vulvar SCCs seem to comprehend the majority of vulvar carcinomas in immunocompromised women.

1.3.5 Genital (pre)malignancies in renal transplant recipients

The role of HPV in the oncogenesis of genital malignancies has urged investigators to theorise that the immunosuppressed state poses transplant patients at risk to HPV infection with subsequent cancer development.

Already in 1975, Porreco et al. described a 14-fold increased incidence of intraepithelial lesions of the cervix in RTRs compared with an age matched group in the general population.[88] In the following years, several other studies showed increased

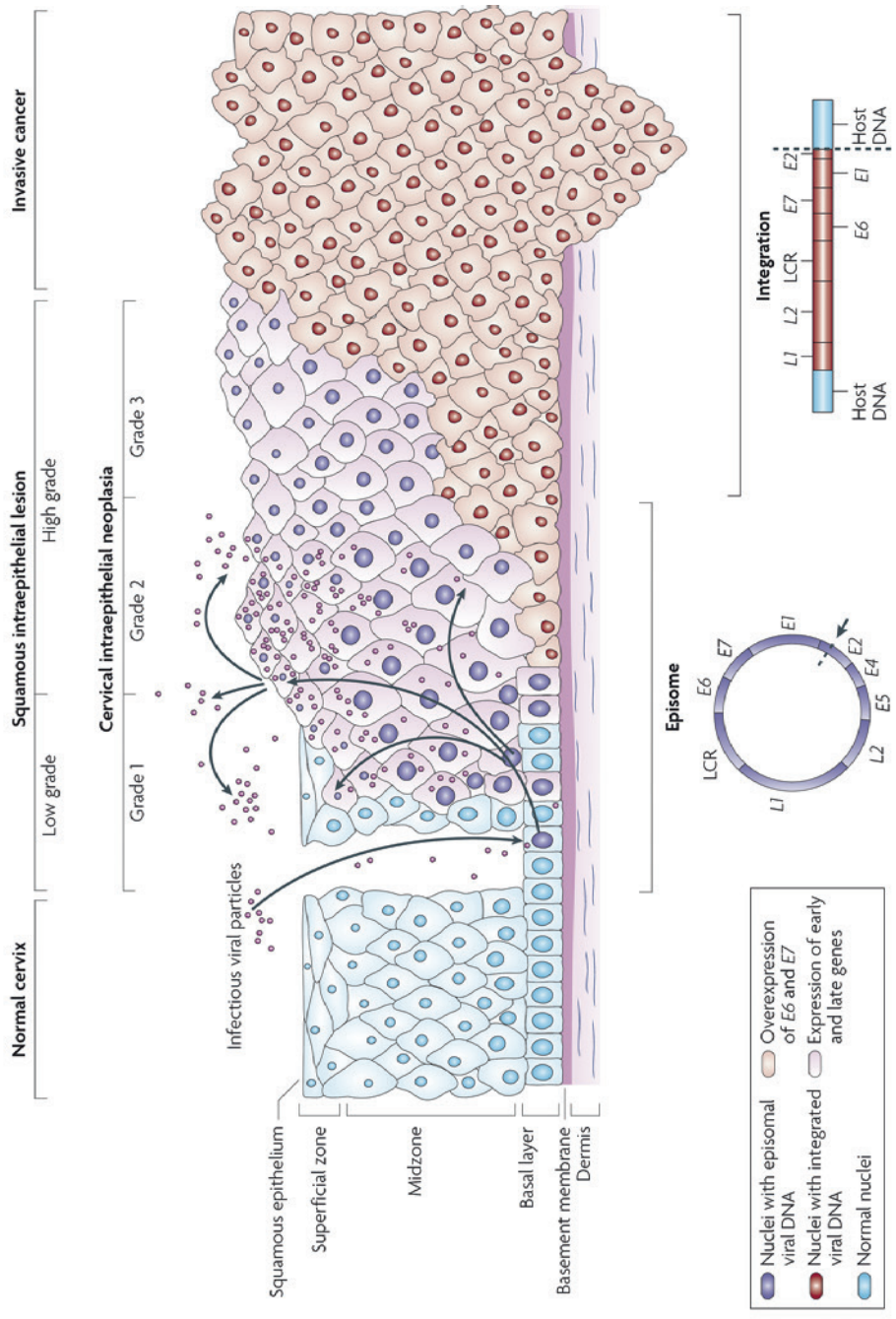

Figure 1 HPV-mediated progression to cervical cancer

Figure 1 HPV-mediated progression to cervical cancer

Basal cells in the cervical epithelium rest on the basement membrane, which is supported by the dermis. Human papillomavirus (HPV) is thought to access the basal cells through micro-abrasions in the cervical epithelium. Following infection, the early HPV genes *E1, E2, E4, E5, E6* and *E7* are expressed and the viral DNA replicates from episomal DNA (purple nuclei). In the upper layers of epithelium (the midzone and superficial zone) the viral genome is replicated further, and the late genes *L1* and *L2*, and *E4* are expressed. L1 and L2 encapsidate the viral genomes to form progeny virions in the nucleus. The shed virus can then initiate a new infection. Low-grade intraepithelial lesions support productive viral replication. The progression of untreated lesions to micro invasive and invasive cancer is associated with the integration of the HPV genome into the host chromosomes (red nuclei), with associated loss or disruption of *E2*, and subsequent up regulation of *E6* and *E7* oncogene expression. LCR = Long control region.

incidences of CIN and cervical cancer after renal transplantation, with standardised incidence rates (SIRs) described between 2.3 and 8.6.[70,73,129-131]

Vulvar (pre)malignancies in RTRs are only sparsely described in the current literature. However, it is known that RTRs have an obviously increased risk for HPV-related vulvar (pre)malignancies.[73,75,76] The ANZDATA Registry, which contains data of more than 13.000 RTRs (110.395 person years) transplanted between 1980 and 2003, reported SIRs varying between 45.6 and 55.8 for vulvar cancer.[74,132]

1.3.6 Treatment and prevention of genital (pre)malignancies in renal transplant recipients

Treatment

Therapeutic concessions are frequently needed in the treatment of genital (pre) malignant lesions in RTRs, as radiation therapy and extensive surgery may damage the renal transplant. Prognosis may therefore be compromised and prevention of these lesions in RTRs is of utmost importance.

Primary prevention

Currently, two vaccines containing immunogens for HPV genotypes 16 and 18 are available in many countries. These vaccines may prevent the majority of HPV 16 and 18 related anogenital (pre)malignancies and have been shown to be highly effective in the general population. The vaccines may also be promising for RTRs although they may have a decline in vaccine-induced immunity.[133]

Secondary prevention
In the Dutch national cervical cancer screening program, women aged between 30 and 60 years are invited for cervical screening every five years. Based on the evidence of the higher risk for malignancies, it is suggested that this screening in the transplantation population should be intensified, although there is no consistent evidence that this will lead to a reduction in cervical cancer incidence and subsequent mortality.[88,134,135] By now, several European and American guidelines (e.g. the European Best Practice Guidelines, the "Kidney Disease: Improving Global Outcomes"-foundation and the American Society of Transplantation) recommend to perform at least annual cervical cancer screening with pelvic examination and cervical smear in female RTRs.[136-138] According to Wong et al., annual screening for cervical cancer using conventional cytology in female RTRs is cost effective when compared with no screening.[139] Additionally, regular surveillance of the anogenital region of female RTRs is important.[137,138] Annual screening for cervical cancer provides an excellent opportunity to perform a thorough external examination of the anal and vulvar regions.

1.4 Outline of this thesis

This thesis includes clinical studies on genital psoriasis and HPV-related anogenital (pre)malignancies in female RTRs. The thesis is divided in two parts.

Part A of this thesis focuses on genital psoriasis. Remarkably little is known about the epidemiology, clinical presentation, impact and therapy of genital psoriasis, although this hidden skin disease will affect a significant proportion of patients with psoriasis at some time during their disease and is a frequent cause of genital complaints.

Specific themes that were studied in this part include:

- epidemiology of genital psoriasis in the Netherlands (chapter 2)
- impact of genital psoriasis on quality of life and sexual health (chapter 3)
- patients' experiences of psoriasis in the genital area (chapter 4)
- effects of specialised care for patients with genital psoriasis (chapter 5)

Part B of this thesis focuses on HPV-related anogenital (pre)malignancies in female renal transplant recipients. As a consequence of the obviously elevated risk for HPV-related anogenital (pre)malignancies in this population and the restrictions in treatment of these lesions, additional attention to screening and prevention of these lesions is required.

Specific themes that were studied in this part include:

- cervical screening in female renal transplant recipients (chapter 6)
- prevalence of gynaecological (pre)malignancies in the female renal transplant recipient population (chapter 6)
- clinical overview of anogenital malignancies in female renal transplant recipients and HPV genotype distribution in these lesions (chapter 7)
- epidemiology of HPV infections in female renal transplant recipients (chapter 8)

Concluding this thesis, in chapter 9 the main findings of the studies are summarised and the implications for patient care are discussed. Future perspectives regarding a multidisciplinary approach for anogenital lesions will be given.

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PART

A

CHAPTER

2

Genital psoriasis: a questionnaire-based survey on a concealed skin disease in the Netherlands

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Abstract

Background

Psoriatic lesions may involve nearly all sites of the body. Involvement of the genital skin is frequently classified as part of intertriginous psoriasis without special awareness and treatment for this presentation of the disease. Gaining knowledge about the frequency of the involvement of genital skin in these patients will improve the overall care for patients with psoriasis.

Objectives

We studied the prevalence of genital psoriasis in the Netherlands and epidemiological characteristics of this specific presentation of the disease. Furthermore, we studied the relation between flexural and genital psoriasis.

Patients/Methods

A self-administered questionnaire was sent to all 5300 members of the Dutch Psoriasis Society. Sociodemographic patient characteristics and disease-related data (such as localisation of psoriatic lesions, involvement of the genitalia, age at onset of genital psoriasis and severity of genital psoriatic lesions) were collected and analysed.

Results

A response rate of 37% was achieved. Almost 46% of the responding patients with psoriasis, that is 16.5% of all potential responders (n = 5300), report genital involvement at some time during the course of their disease. The genitalia can become affected at any age. Many patients with current genital involvement (38%) do not have the flexural skin affected.

Conclusions

A large part of patients with psoriasis suffer from genital psoriasis, which was not associated with flexural involvement in at least one third of them. More attention to the genital region is required in the current standard treatment of both male and female psoriatic patients at any age.

Introduction

Psoriasis is a multifactorial, chronic, immune-mediated hyperproliferative inflammatory skin disease with a relatively high prevalence in the general population of about 2%.[1-4] The most common type of psoriasis is chronic plaque psoriasis which preferentially involves the scalp and the outer aspects of the elbows and knees.[4] However, psoriatic lesions may involve all sites of the body, such as the intertriginous areas (synonym: flexures) and the genital skin.

Intertriginous psoriasis is diagnosed when the major skin folds of the body are affected. Areas that may be involved are the axillae, retroauricular folds, groins, gluteal clefts and submammary folds. Involvement of the genital skin is frequently classified as part of intertriginous psoriasis and there is often no special awareness for this presentation of psoriasis. However, genital psoriasis deserves a distinct approach as it may be associated with considerable morbidity, discomfort and embarrassment. The genital skin changes from stratified and keratinised squamous cell epithelium to mucosa.[5-7] Treatment of genital psoriatic lesions deserves special attention, as the vulnerable and thin genital skin has a high sensitivity and there might be an increased penetration of topical modalities in the genital area.[5]

Psoriatic lesions at the genitalia often present as well-demarcated, bright erythematous, thin plaques and these usually lack the typical scale which is apparent at other parts of the body, because of maceration.[8-18] However, scales might be seen at the more keratinised surfaces of the genital skin (i.e. penile shaft, scrotum and adjacent to the labia majora).[18-20] When scaling is present, it is often minimal and can easily be scraped off, leaving pinpoint bleedings (Auspitz phenomenon).[9,10,21,22] In addition to plaque-type genital psoriasis, the genital area might be involved with pustular psoriasis as well.[23,24]

Remarkably few data exist on the involvement of the genitalia in patients with psoriasis, leaving the current prevalence of genital psoriasis unclear. Three dated surveys in populations of patients visiting the dermatologist (conducted between 1964 and 1974) reported that involvement of the genitalia might occur in 29-40% of the patients.[25-27] There are only two recent surveys that provide information on the prevalence of genital psoriasis while the primary focus of these studies were on other issues: the first investigation[28] assessed patient compliance in the treatment of psoriasis and the other study[29] evaluated patient perspectives on the impact of psoriasis. Nevertheless, involvement of the genitalia was reported in 29 and 32% of the patients respectively.[28,29]

Genital psoriasis is probably more common than previously thought. Patients might feel embarrassed about genital discomfort (patients' delay). In addition, anamnesis on genital complaints and inspection of intimate body regions of patients are often omitted from physical routine examination in dermatological outpatient clinics

(doctors' delay). Similarly, healthcare professionals infrequently initiate a dialogue on sexual (dys-) function and the majority of psoriatic patients have never been asked about their sexual life by their attending doctor.[30-32] Accordingly, the problem of genital psoriatic lesions may remain unnoticed in psoriatic patients.

It is well known that psoriasis may have a major impact on the quality of life.[33-36] Involvement of the genitalia might have a more profound impact on the patient's quality of life with considerable impairment of psychosexual appreciation as well.[36]

To improve the care for patients with psoriasis, it is necessary to acquire knowledge about the frequency of the involvement of genital skin in these patients. The aim of this study is to evaluate the prevalence of genital psoriasis in the Netherlands and to describe epidemiological characteristics of this specific presentation of psoriasis.

Materials and Methods

Patients

A self-administered questionnaire was distributed to all members (n = 5300) of the Dutch Psoriasis Society together with an introduction letter and reply-paid envelopes. The questionnaire could be completed anonymously and no incentives were given. A special trained advisor of the Dutch Psoriasis Society could be contacted by telephone when patients had questions about the investigation. For difficult issues, consultation of one of the investigators was advised. After receiving the questionnaires, personal data were separated from the questionnaires and both items were assigned an identification number for data handling and control, as well as for storing and retrieving the questionnaires during subsequent surveys. Data were analysed anonymously.

Study design

The investigation was conducted as from the 14th of February 2009 and responses were accepted through the first of June 2009. Prior to the distribution of the questionnaires, we conducted a pilot study on 10 patients to improve the quality and efficiency of the survey. Items about sociodemographic patient variables (age, gender, weight and length) and medical data (medical history, age at onset of psoriasis and at diagnosis, self-reported localisation and severity of psoriatic lesions, type of psoriasis, involvement of the genitalia, age on which genital psoriasis started and severity of genital lesions) were covered in the questionnaire. The severity of psoriasis was assessed in multiple-choice questions (by using an ordinal scale; classification: no, mild, moderate or severe lesions) and by the self-administered psoriasis area and severity index (SAPASI). SAPASI is a valid and reliable instrument that allows patients to assess the severity of their psoriasis. The redness, induration and scaliness of an average psoriatic lesion are rated with three visual analogue

scales. The involved area of the skin is marked on an anatomical sketch and is weighted by an investigator according to the original PASI score.[37] The range of SAPASI is 0-72, with increasing severity of psoriasis with increasing SAPASI scores. Ranges to explain the severity of psoriasis were previously described as: 0, complete remission; > 0 to 3, mild; > 3 to 15, moderate; > 15, severe.[38]

Statistical analysis

All answers were entered in a database and subsequently statistical calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA). Continuous variables were described using median (and ranges) or mean (± standard deviation), depending on the (non-) parametric distributions of measured variables. Discontinuous variables were described by the total frequencies and percentages of each modality. Independent Student's t-tests were used to calculate the significance of differences between numeric variables and chi-square (X^2) tests were used for differences between categorical variables. P-values of <0.05 were considered to be statistically significant. Calculations were only performed on the total number of patients who answered the concerning queries. Missing values were not included in the analysis.

Results

Of the 5300 questionnaires sent, 1963 were returned, representing an overall response rate of 37%. Twenty responses were excluded as the respondents were less than 18-years of age (n = 18) or because the gender of the patient was unknown (n = 2). The remaining 1943 responses were suitable for analysis.

Baseline

The distribution of baseline characteristics according to gender, age, BMI and SAPASI is reported in Table 1. The respondents comprised 1008 women (51.9%) and 935 men (48.1%). The mean age of the respondents was 56.3 years (±13.5 years), with the men being slightly older [mean age 57.6 years (±12.4 years)] than the female patients [mean age 55.1 years (±14.3 years)] (t-test: $P < 0.001$). The average BMI of all the respondents was 26.6 kg/m^2 (±4.6 kg/m^2). This was comparable for both men and women. According to the BMI classification of the World Health Organisation (WHO),[39] 39.6% of the patients had a normal weight (BMI 18.5 – 24.9) and 59.9% had overweight (BMI ≥ 25) with 17.6% being (morbid) obese (BMI ≥ 30).

The self-reported mean age at onset of psoriasis was 25.4 years (±15.3 years), varying between 0 and 79 years of age (see Table 1). The vast majority of the respondents (98.6%) (n = 1915) stated that their psoriasis was diagnosed by a general physician

Table 1 Baseline characteristics

Baseline characteristics		
Sex, No. (%)		
Male	935	48 %
Female	1008	52 %
Age, years		
Mean (± SD)	56.3	± 13.5
Age at onset of psoriasis, years		
Mean (± SD)	25.4	± 15.3
Duration of psoriasis, years		
Mean (± SD)	30.9	± 16.0
BMI, kg/m^2		
Mean (± SD)	26.6	± 4.6
SAPASI score		
Median (range)	6.0	0-39.4
Psoriasis, No. (%)		
With nail involvement	992	51.1 %
With joint complaints	824	42.4 %

No. = Number; SD = Standard deviation; BMI = Body mass index; SAPASI = Self-administered psoriasis area and severity index

or a medical specialist. The remaining 1.4% (n = 28) did not answer this particular query. Psoriasis was diagnosed after a mean of 2.1 years after the beginning of complaints, with a maximum of 59 years thereafter. Most respondents (90.4%) were diagnosed with psoriasis within the first 5 years after the beginning of skin complaints. The mean duration of the respondents' psoriasis was 30.9 years (±16.0 years). Patients had a median SAPASI score of 6.0 ranging from 0 to 39.4 (mean: 6.6 ± 4.4). Chronic plaque psoriasis was the most common clinical type of psoriasis, which was present in 1313 cases (67.6%). More than half of the respondents (51.1%) reported nail involvement. In addition, joint complaints were present in 42.4% of the patients.

Genital psoriasis

Of the 1926 respondents, who answered the query, 877 patients (45.5%) stated that their genital skin had been affected by psoriasis at sometime during the course of their disease. This corresponds to 16.5% of the entire study population (n = 5300). Genital psoriasis significantly prevailed in male patients compared with female

patients: 497 (53.3%) patients of the male sample (n = 932) indicated genital involvement during the disease, whereas 380 patients (38.2%) of the female sample (n = 994) indicated genital involvement (X^2: $P < 0.001$).

More than one-third of the patients (569 of 1621 patients, 35.1%) stated that they suffered from genital psoriasis at the moment of this study, with varying degrees of severity [mild (82.6%), moderate (15.1%) or severe (2.3%)].

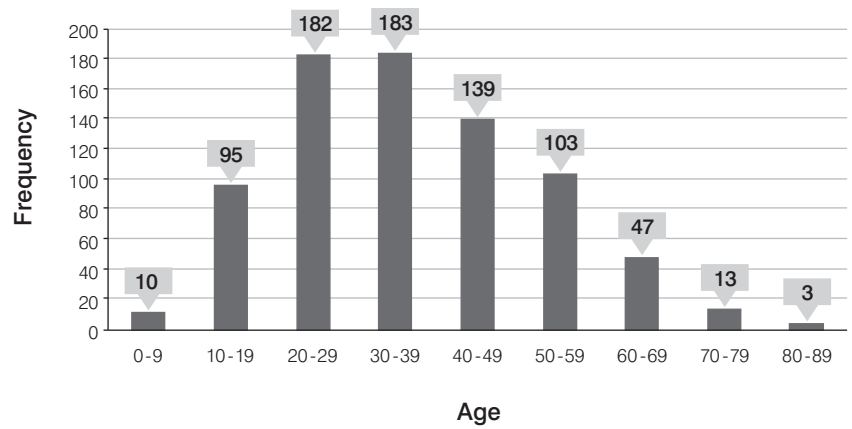
There were no significant differences in the presence of overweight/obesity (BMI ≥ 25) for patients with and patients without genital psoriasis (X^2: P = 0.44).

Age at onset of genital psoriasis

The mean age at onset of genital psoriasis appeared to be 35.3 years (±15.0 years). However, psoriatic involvement of the genital skin may begin at almost any age, regarding the broad range reported by the patients (range: 3-85 years of age). Figure 1 shows the distribution of age at onset of genital psoriasis, reflecting that the majority of patients had the first genital manifestation between 20 and 40 years. No significant differences in age at onset of genital psoriasis existed between men and women (t-test: P = 0.80).

The median time between the onset of psoriasis and the onset of genital lesions appeared to be 8.0 years, ranging from 0 to 66 years. One hundred and thirty-six patients (17.7%) had genital involvement as initial presentation of their psoriasis.

Figure 1 Age at onset of genital psoriasis

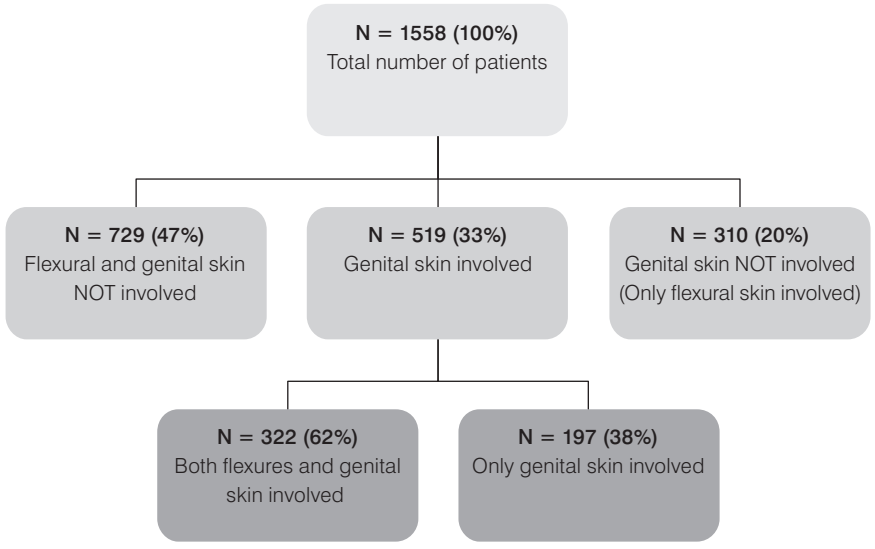


Flexural versus genital psoriasis

Responses of 1558 patients about current involvement of the genitalia and flexures, regardless whether other sites of the body (e.g. trunk, extremities or scalp) were affected at that time, are shown in Figure 2. This question was answered by 1558 patients, of which 519 patients (33.3%) currently have genital psoriasis. Of these, 197 patients (38.0%) had only genital psoriasis without having the flexures affected.

Three hundred and four of the 310 patients in whom currently only the flexural skin is affected by psoriasis answered the query on whether they had had genital involvement during the course of their disease. Two hundred and thirty-four (234) of these patients (77.0%) answered that they had never had their genital skin affected with psoriasis.

Figure 2 Current genital and/or flexural involvement



N = Number

Discussion

Our study illustrates that almost 46% of the patients with psoriasis report genital involvement at some time during the course of their skin disease. The mean age at onset of genital psoriasis is 35.3 years, but the genitalia may be involved at nearly any age. Almost 40% of patients with current genital involvement do not have the flexural skin affected. Additionally, a substantial part of the population had flexural psoriasis

without ever the genital area having involved. This indicates that flexural and genital psoriasis are most probably distinct manifestations of psoriasis.

The large number of patients responding to our questionnaire (1943 patients) provides valuable insights into the epidemiology of genital psoriasis, which is a presentation of psoriasis with limited attention of professionals until now. Nearly half of our patients reported involvement of the genitalia during the course of their disease, which is the highest percentage ever reported in the literature. However, it is remotely possible that patients with genital involvement may have returned the questionnaires preferentially (sampling bias). Nevertheless, even when we assume that all non-responders would have no genital involvement, still 16.5% of the population has genital psoriasis. The truth most probably lies somewhere in between.

Three previous studies reported genital manifestations of psoriasis in 29–40% of the patients.[25-27] Remarkably, these studies which were published approximately 40 years ago have never led to further publications in the field of the genital manifestations of psoriasis. Two recent studies report involvement of the external genitalia in 29 and 32% of the patients, but these numbers were just secondary outcome measures.[28,29]

It is difficult to understand why direct questioning to genital complaints and active inspection of the external genital area in patients with psoriasis has not become a part of daily practice for dermatologists after the publications about high prevalence of genital psoriasis. The impact of genital psoriasis on quality of life and psychosexual appreciation may be apparent.[36] The negative influence on psychosexual wellbeing and quality of life may be caused by either the skin disease itself and/or the localisation of psoriatic lesions at genital skin. Unfortunately, the prevalence of genital psoriasis is underestimated, because of both patients' and doctors' reluctance. The implementation of adequate information on genital psoriasis in (self-) educational programmes for patients with psoriasis might be of interest to require more common knowledge about this intimate manifestation of the disease. Moreover, doctors should be encouraged to initiate a dialogue about possible genital complaints to offer adequate treatment and psychosexual counselling by professionals.

Our results showing that almost 60% of the respondents had a BMI ≥ 25 (which is defined as overweight by the WHO[39]) are in agreement with the previous studies that have shown a positive association between increased BMI and psoriasis.[40,41] There is no significant difference in the presence of overweight/obesity between patients with and patients without genital psoriatic lesions.

The mean age at onset for psoriasis in general was 25.4 years. The median time between onset of psoriasis in general and onset of genital lesions turned out to be 8 years, with a broad range. This difference in ages at onset is difficult to explain. Apparently, as the peak incidence of genital lesions is after menarche and before menopause in females, an association between the occurrence of genital lesions and hormonal factors is improbable.

It is evident from this study that there are significantly more male patients with psoriasis of the external genitalia (53.3% of the male population) compared with female patients (38.2% of the female population). Our data reconfirm the discrepancy between male and female genital involvement which is already documented in older studies on the epidemiology of psoriasis. Three previous studies reported data on male and female genital psoriatic involvement, which appeared to be present in 33–49% and 21–33% of cases respectively.[25-27] Interestingly, our percentages are by far the highest percentages ever documented. It is attractive to speculate on the preponderance of male patients with genital psoriasis. Male genital skin may be affected more often with psoriasis than female genital skin and/or males may report these lesions more often. However, two other explanations may be more likely: inspection of the external genitalia is easier for males compared with females; moreover, complaints of female external genitalia might be more difficult to interpret correctly by the women as a result of confusion with other genital dermatoses (like non-specific dermatitis or candidiasis). Nevertheless, male and female patients are both frequently involved with genital psoriatic lesions.

The external genital skin is generally classified as flexural skin, although it forms a unique area comprising different structures and types of epithelium.[5-7] As a consequence of local circumstances, the genital skin folds are susceptible to maceration and fissuring and the normal characteristics of psoriasis might be lost or modified in this region. Additionally, as a result of the localisation, genital lesions might be confused with sexually transmitted diseases. The present study revealed that flexural and genital psoriasis were separate manifestations in a considerable number of patients: 38% of the patients with current genital psoriasis did not have the flexures affected and 77% of the patients with current flexural psoriasis had never experienced genital lesions. Based on these percentages and the typical presentation of psoriasis at genital skin, it is reasonable to assume that flexural and genital psoriasis are distinct entities of psoriasis that both require special attention in clinical practice.

A selection bias might be created by questioning the members of the Dutch Psoriasis Society, as members of a patient support association may possibly not represent a random sample of patients with psoriasis. It may be speculated that these patients are perhaps more interested or worried about their disease or they might suffer from more severe psoriasis. The possibility to answer the questionnaire anonymously is an important strength of our investigation. Patients probably indicate genital symptoms more easily on an anonymous questionnaire than during a visit at the outpatient clinic. As our questionnaire based study asked retrospectively for information, a slight recall bias might be present in our data, which can cause either an over- or underestimation of the results. Bearing in mind the multiple differential diagnoses for genital psoriasis, we deliberately asked for the presence of ‘psoriatic

lesions at the genital skin’ instead of ‘genital complaints in general’. At least 98.6% of the respondents was diagnosed with psoriasis of their skin by a general physician or a medical specialist. We assume that most patients with psoriasis will recognise their skin disease on genital skin rather adequate, although it might be possible that other skin diseases than psoriasis have been present at the genital skin of the respondents.

To conclude, our study shows that a large part of patients with psoriasis suffer from genital presentation of this disease and that genital psoriasis is most likely another entity than flexural psoriasis. To our opinion, these results plead for more attention to the genital region in both males and females with psoriasis at any age. A challenging task for further research is to conduct a prospective study to investigate whether genital complaints in psoriatic patients are actually caused by genital psoriasis. Additionally, treatment options for this presentation of psoriasis should be studied. Moreover, the impact of genital psoriasis on psychosexual satisfaction and quality of life should be part of further research.

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CHAPTER

3

Quality of life and sexual health in patients with genital psoriasis

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Abstract

Background
Knowledge about quality of life and sexual health in patients with genital psoriasis is limited.

Objectives
We studied quality of life and sexual function in a large group of patients with genital psoriasis by means of validated questionnaires. In addition, we evaluated whether sufficient attention is given by healthcare professionals to sexual problems in patients with psoriasis, as perceived by the patients.

Methods
A self-administered questionnaire was sent to 1579 members of the Dutch Psoriasis Association. Sociodemographic patient characteristics, medical data and scores of several validated questionnaires regarding quality of life (Dermatology Life Quality Index) and sexual health (Sexual Quality of Life Questionnaire for use in Men, International Index of Erectile Function, Female Sexual Distress Scale and Female Sexual Function Index) were collected and analyzed.

Results
This study ($n = 487$) shows that psoriasis has a detrimental effect on quality of life and sexual health. Patients with genital lesions reported even significantly worse quality of life than patients without genital lesions (mean ±SD quality of life scores 8.5 ± 6.5 vs. 5.5 ± 4.6, respectively, $P < 0.0001$). Sexual distress and dysfunction are particularly prominent in women (reported by 37.7% and 48.7% of the female patients, respectively). Sexual distress is especially high when genital skin is affected (mean ±SD sexual distress score in patients with genital lesions 16.1 ± 12.1 vs. 10.1 ± 9.7 in patients without genital lesions, $P = 0.001$). The attention given to possible sexual problems in the psoriasis population by healthcare professionals is perceived as insufficient by patients.

Conclusions
In addition to quality of life, sexual health is diminished in a considerable number of patients with psoriasis and particularly women with genital lesions have on average high levels of sexual distress. We underscore the need for physicians to pay attention to the impact of psoriasis on psychosocial and sexual health when treating patients for this skin disease.

Introduction

Psoriasis may involve all sites of the body, including the genital skin. Psoriatic lesions at the genitalia often present as well-demarcated, bright erythematous, thin plaques and these usually lack the typical scale which is apparent at other parts of the body, due to maceration.[1-7] Only rarely may scaling be seen at the genital skin. Then, it is often minimal and can easily be scraped off, leaving pinpoint bleeding.[7-9] In addition to plaque-type genital psoriasis, the genital area might also be involved with pustular psoriasis.[10,11] Treatment of genital psoriatic lesions deserves special attention, as the vulnerable and thin genital skin is highly sensitive and there might be an increased penetration of topical treatment agents in the genital area.[12] Despite the possibility of adequate treatment, (genital) psoriasis is characterised by exacerbations and remissions. A substantial number of patients with psoriasis have genital psoriatic lesions. We recently published data on the prevalence of this particular localisation of psoriasis in patients in the Netherlands. Of 1943 patients with psoriasis, over 45% reported genital presentations of psoriasis at some time during the course of their disease.[13]

It is well known that psoriasis may have a substantial negative impact on physical, psychological and social dimensions of quality of life.[14-18] The impact of psoriasis on sexual health, which is an integral part of general health and quality of life, is an underexplored area. There are only few studies on this topic, relying on data from small samples. According to these studies, sexual health may frequently be impaired in patients with psoriasis compared with people with healthy skin.[19-24] Although the literature is not uniform, it is conceivable that when psoriasis is present on the more sensitive areas of the body, like the genital skin, the negative effect on sexual quality of life is more profound. This was established by Buckwalter in 1982.[25] However, van Dorssen *et al.* found no correlation between diminished sexual satisfaction and localisation of psoriasis on genital skin.[26] One more recent publication denotes that patients with a decreased sexual activity since the onset of psoriasis reported a marginally, but not significantly, greater psoriasis severity affecting the genital area compared with patients without a decreased sexual activity.[20] Not only psoriasis itself but also the treatments as used by the patients may cause sexual dysfunction; some publications report that antipsoriatic medication (i.e. methotrexate and etretinate) might cause sexual impotence and erectile dysfunction.[27-29] In addition, itch and related scratching behaviour might have a particular worsening impact on the genital skin, resulting in a vicious itch-scratch circle that worsens the condition of the affected psoriatic genital skin.[30] Despite this possible impact of psoriasis on intimate relationships and sexuality, the vast majority of patients with a chronic skin disease like psoriasis reported that they had never been asked about their sexual life by their attending doctor.[22]

The aim of our study was to gain more knowledge about quality of life and sexual function by means of validated questionnaires in a large group of patients with genital psoriasis. In addition, we evaluated whether sufficient attention is given by health care professionals to sexual problems in patients with psoriasis, as perceived by the patients.

Materials and methods

Subjects and procedure

In total, 1579 members of the Dutch Psoriasis Association were asked to participate in the study. These patients were involved in a previous study on epidemiology of genital psoriasis[13] and had given their permission to participate in a consecutive questionnaire-based study on quality of life and sexual health. Medical ethics review was not required according to the local Medical Review Ethics Committee. All patients were ≥ 18 years of age. Participants had the opportunity to consult one of the investigators by e-mail for questions regarding the study. Repeat mailings were made for unreturned surveys. We introduced a secured digital answering system for electronic completion of the questionnaire. Besides, a paper version was available for those patients without access to the internet. Results were collected between 24 September 2009 and 31 December 2009. Answers were processed anonymously and data were linked to the corresponding answers of the preceding survey by an identification number.

Study design

Contents of the first questionnaire have previously been described in detail.[13] The following items of that questionnaire were used for the current study: medical data (background information on psoriasis, severity of psoriasis and current or previous genital involvement), Dermatology Life Quality Index (DLQI) scores and Self-Administered Psoriasis Area and Severity Index (SAPASI) scores. As psoriasis is a chronic and fluctuating skin disease, we modified the time frame of the DLQI towards 1 year. Therefore, all DLQI scores mentioned are for the modified 1-year basis DLQI.

The secondary questionnaire comprised several validated instruments to measure sexual health [Sexual Quality of Life Questionnaire for use in Men (SQoL-M), International Index of Erectile Function (IIEF), Female Sexual Distress Scale (FSDS) and Female Sexual Function Index (FSFI)]. ter Kuile *et al.* replicated the adequate psychometric properties of the FSDS and FSFI within a Dutch population and the SQoL-M and IIEF have also been validated in the Dutch population.[31-33] All questionnaires are based on the patients' experiences over the previous 4 weeks. Just like the DLQI, we deliberately modified all questionnaires so that all responses were based on the experiences over the previous year. Patients were also asked for

several sociodemographic patient characteristics (age, gender and marital status) and subjective feelings regarding sexuality and having psoriasis: whether there is sufficient attention given to possible sexual problems and whether more attention to these problems is required (by checking 'yes', 'no', 'unknown'). Moreover, patients were asked whether they believe that since the onset of psoriasis sexual activity has declined. If yes, we asked the patients to rate (using a four-point scale of 'never', 'sometimes', 'often', and 'always') the frequency with which several factors affected their sexual functioning, as was previously described by Gupta and Gupta.[20]

Scoring systems

See Table 1 for an overview of all scoring systems used.

Table 1 Scoring systems

Scoring System	Measure	Interpretation
DLQI	Dermatology-specific QoL	↑ score = ↓ QoL
SAPASI	Severity of psoriasis	↑ score = ↑ severity
SQoL-M	Male sexual QoL	↑ score = ↑ QoL
IIEF	Male sexual function	↑ score = better sexual function
FSDS	Female sexually related personal distress	↑ score = ↑ distress
FSFI	Female sexual function	↑ score = better sexual function

QoL = Quality of life

Dermatology Life Quality Index

The DLQI is a commonly used 10-item questionnaire regarding the quality of life in patients with a skin disease, comprising the following six domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. The total score is calculated by summing the score of each question, resulting in a minimum of 0 and a maximum of 30. In cases of missing answers, we calculated the scores according to the manual. The higher the DLQI score, the more quality of life is impaired.[34]

Self-administered Psoriasis Area and Severity Index

This instrument allows patients to assess the severity of their psoriasis. Patients rate the redness, induration and scaliness of an average psoriatic lesion with three visual

analogue scales and shade the involved area of their skin on a silhouette of the human body. Based on the silhouette shading, an investigator assigns a value for each area.[35] The SAPASI weights the involved area as in the original Psoriasis Area and Severity Index[36] score. The range of SAPASI is 0–72, increasing SAPASI scores indicating increasing severity of psoriasis. Ranges to explain the severity of psoriasis were previously described as: 0, complete remission; >0 to 3, mild; > 3 to 15, moderate; > 15, severe.[37]

Sexual Quality of Life Questionnaire for use in Men

The SQoL-M is a self-administered instrument which assesses sexual quality of life in men.[32] The instrument contains 11 items, each with a response scale ranging between 'completely agree' (1 point) and 'completely disagree' (6 points). Total scores were calculated according to the SQoL-M scoring manual.[32] The total score ranges from 0 to 100; increasing scores indicate increase in quality of life.

International Index of Erectile Function

The IIEF is a multidimensional, 15-item questionnaire scale for the assessment of relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction), with good psychometric properties.[33] The five domains are each set up by a different cluster of items and summing the scores for individual items computes domain scores.[33]

Any missing response resulted in the questionnaire being excluded from the final calculation of the questionnaire, according to the IIEF scoring manual. The total score ranges between 5 and 75; higher scores indicate better sexual function.

Female Sexual Distress Scale

The FSDS is a reliable and psychometric valid 12-item scale that assesses sexually related personal distress in women.[31,38] The total score ranges from 0 to 48, with higher scores indicating a higher level of sexual distress. Questionnaires were excluded from analyses when more than 10% of the answers were missing. A total score of ≥ 15 on the FSDS is the recommended cutoff score to establish the presence of sexually related personal distress.[38]

Female Sexual Function Index

The FSFI measures key dimensions of female sexual function.[31,39] The questionnaire is composed of 19 items, with six individual domains (sexual desire, arousal, lubrication, orgasm, satisfaction and pain). Calculations were performed as previously described by Rosen *et al.*[39] A domain score was not calculated whenever one or more items of the domain were missing. Full-scale scores were calculated by adding the six domain scores. To calculate this score, a maximum of one domain score was

allowed to be missing. The full-scale score ranges between 2 and 36. Higher scores of the FSFI mean better sexual functioning. A FSFI total score of 26.55 or less is the cutoff point for differentiating women with and without sexual dysfunction.[40]

Statistical analysis

All answers were entered in a computerised database. Subsequently, statistical calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA). Data of all measured variables were checked for their distribution pattern.

Continuous variables were described as median and range or mean ±SD, depending on the (non)parametric distributions of variables measured. Discontinuous variables were described by the total frequencies and percentages of each modality. Missing values were processed as described in the section 'scoring systems'; for other variables the missing data were not included in the analysis.

Differences between groups were examined using a chi-square test for categorical variables. Parametric distributed continuous variables were compared by using independent Student's *t*-tests and nonparametric distributed continuous variables were compared using the Mann-Whitney *U*-test. Correlations between different variables were calculated using Pearson or point-biserial correlation tests. We used a partial correlation test, controlling for SAPASI scores, for calculation of the correlation coefficients between scores of questionnaires and having current genital psoriasis. Statistical significance was achieved at $P < 0.05$.

Results

Baseline

In total, 487 questionnaires were returned, resulting in a response rate of 31%. Baseline characteristics are shown in Table 2.

Significantly more men (278 responders out of 776; 35.8%) responded to our questionnaire compared with women (209 responders out of 803; 26.0%) [X^2: $P < 0.0001$]. Respondents were significantly younger (53.3 vs. 57.3 years; independent Student's *t*-test: $P < 0.0001$), were diagnosed with psoriasis at a significantly younger age (24.5 vs. 26.2 years; independent Student's *t*-test: $P = 0.03$) and had a significantly higher SAPASI score (7.1 vs. 6.6; independent Student's *t*-test: $P = 0.04$) compared with non-respondents.

The mean ± SD age of the patients at the time of the second questionnaire was 53.9 ± 12.3 years. The mean ± SD age at disease onset was 24.5 ± 14.0 years. More than one-third of the patients (38.2%) experienced psoriatic skin lesions before the age of 18 years. The majority of respondents had chronic plaque psoriasis (69.6%),

Table 2 Baseline characteristics

Sex, n (%)		
Male	278	(57.1%)
Female	209	(42.9%)
Marital status, n (%)		
Single	42	(8.6%)
Married/cohabiting	406	(83.4%)
Other[a]	39	(8.1%)
Age (years), mean ± SD	53.9	(± 12.3)
Psoriasis, n (%)[b]		
Plaque	339	(69.6%)
Guttate	183	(37.6%)
Pustular	23	(4.7%)
Erythrodermic	28	(5.7%)
With joint involvement	208	(42.7%)
With nail involvement	270	(55.4%)
Age at onset of psoriasis (years), mean ± SD	24.5	(± 14.0)
SAPASI score, median (range)	6.4	(0 - 39.4)
Ever had genital psoriasis, n (%)		
Yes	277	(56.9%)
No	210	(43.1%)
Age at onset of genital psoriasis (years), mean ± SD	34.7	(± 14.1)
Current genital psoriasis, n (%)		
Yes (GEN)	172	(36.8%)
No (NGEN)	296	(63.2%)

[a] Divorced, widowed, separated or living apart together
[b] One patient may have several types of psoriasis
N = Number; SD = Standard deviation; SAPASI = Self-administered psoriasis area and severity index; GEN = Group with current genital lesions; NGEN = Group without current genital lesions

followed by guttate psoriasis in 183 (37.6%) patients. The current SAPASI score ranged between 0 and 39.4 (median 6.4). This is comparable with the SAPASI score of the patients in the previous study ($n = 1579$).

In total, 277 patients (56.9%) had their genital skin involved with psoriasis during the course of their disease. The reported mean ± SD age at onset of genital lesions was 34.7 ± 14.1 years (range 3-74). The total group of respondents was divided into two groups according to the presence of current genital lesions. 'Current genital lesions' was defined as follows: genital skin affected by psoriasis at least 6 months before the second questionnaire (i.e. at the time of the first questionnaire). Of the 468 patients who answered the query, 172 patients stated that they had current genital

lesions (GEN group) and 296 patients did not have current genital lesions (NGEN group). Within the NGEN group 86 patients had had genital lesions in the past. In 19 patients we lack information on the presence of current genital lesions; these patients were excluded from comparative analysis between the two groups. Respondents appeared to have current genital involvement significantly more often (172 of 468; 36.8%) compared with nonrespondents (284 of 1053; 27.0%) [X^2: $P < 0.0001$].

Quality of life

The mean ± SD DLQI score of all patients was 6.6 ± 5.5. Table 3 shows the DLQI scores of both groups. Both the total DLQI score as well as all domain scores indicate that patients with current genital lesions experienced significantly worse quality of life than patients without genital psoriatic lesions. There was a small but significant correlation between the DLQI scores and having genital psoriatic lesions [$r = 0.26$, P (two-tailed) < 0.0001].

The responses of the patients on the particular DLQI item concerning sexual life ('Over the last year, how much has your skin caused any sexual difficulties?') showed a significant difference between the GEN group (mean ± SD 0.7 ± 0.9) and the NGEN group (mean ± SD 0.3 ± 0.6) (independent Student's *t*-test: $P < 0.0001$). Male and female respondents did not respond differently to this query (independent Student's *t*-test: $P = 0.22$).

Mean ± SD SAPASI scores differed significantly between the GEN (8.7 ± 5.5) and NGEN (6.1 ± 3.9) group (Mann-Whitney *U*-test: $P < 0.0001$). Nevertheless, the correlation between DLQI scores and having current genital lesions was significant ($r = 0.17$, P (two-tailed) < 0.0001), even when correcting for SAPASI scores. This indicates that genital psoriasis can significantly affect quality of life, independent from the SAPASI score.

Patients from the NGEN group who had had genital psoriatic lesions in the past had the same mean ± SD DLQI score (5.6 ± 4.3) as the patients from the NGEN group who had never had genital lesions (5.5 ± 4.7) (independent Student's *t*-test: $P = 0.87$). Their mean score differed significantly from the mean DLQI scores of the GEN group (5.6 vs. 8.5, $P < 0.0001$).

Sexual health

Men with psoriasis had mean ± SD total scores for the SQoL-M and for the IIEF of 77.2 ± 24.1 and 55.7 ± 17.2, respectively. Patients with genital lesions showed no significantly different scores on both questionnaires compared with patients without current genital lesions. Also, evaluation of domain scores of the IIEF showed no significant differences between both male groups.

Using the FSDS cutoff score of ≥ 15, 37.7% of the women with psoriasis showed sexual distress. Women with current genital lesions showed significantly more sexual

distress (mean ± SD FSDS score 16.1 ± 12.1) compared with women without current genital lesions (mean ± SD FSDS score 10.1 ± 9.7) (independent Student's *t*-test: $P = 0.001$). Besides, the prevalence of sexually related personal distress (FSDS score ≥ 15) was 50.8% in the GEN women and 32.1% in the NGEN women (X^2: $P = 0.01$). SAPASI scores did not influence the correlation between FSDS scores and having current genital lesions. Although not statistically significant, patients from the NGEN group who had had genital psoriatic lesions in the past had a mean ± SD FSDS score (12.9 ± 11.5) between that of patients who had never had genital lesions (9.2 ± 9.1) (independent Student's *t*-test: $P = 0.07$] and that of patients with current genital lesions (independent Student's *t*-test: $P = 0.25$).

The FSFI cutoff score of ≤ 26.55 shows that 48.7% of the women with psoriasis had sexual dysfunction. The presence of sexual dysfunction was equally distributed between the women with genital lesions (31 of 56 patients; 55.4%) and those without genital lesions (57 of 125 patients; 45.6%) (X^2: $P = 0.23$). Besides, the mean scores on the FSFI questionnaire (both total score as well as domain scores) did not show significant differences between both patient groups. See Table 4 for all sexual health scores.

Patient age at onset of genital psoriasis showed a negative correlation with the total scores of the FSFI ($r = -0.24$, $P = 0.03$) and the IIEF ($r = -0.41$, $P < 0.0001$), indicating that patients who were older at onset of genital psoriasis had lower mean scores on these questionnaires, meaning worse sexual functioning. The age at onset of genital psoriasis did not correlate with the mean total scores of the FSDS, SQoL-M and the DLQI questionnaires.

Decline of sexual activity

Of the 481 patients with psoriasis who answered the query concerned, 120 patients (24.9%) answered that their sexual activity declined after the onset of psoriasis. This was seen more in women (32.8%) than in men (19.1%) (X^2: $P < 0.0001$). Table 5 reflects the different factors associated with this decline in sexual activity according to the patients. 'Negative effect of psoriasis on physical appearance', 'diminished sexual desire of the patient', 'inconvenience caused by scaliness of skin' and 'inconvenience caused by topical therapy' were mentioned most frequently.

Attention given to possible sexual problems

Table 6 shows that not more than 9% of the responders ($n = 44$) believe that there is sufficient attention given to possible sexual problems by their doctor. In contrast, at least 43% of all patients ($n = 211$) think that it might be desirable during consultations for healthcare professionals to direct more attention to and more frequently ask about possible sexual problems.

Table 3 Dermatology Life Quality Index (DLQI) scores (mean ± SD) of the two study groups

Group	N	Total DLQI	Personal relations	Symptoms and feelings	Daily activities	Leisure	Work and school	Treatment
GEN	172	8.5 ± 6.5	1.2 ± 1.5	2.9 ± 1.5	1.7 ± 1.7	1.4 ± 1.8	0.4 ± 0.8	0.9 ± 1.0
NGEN	294	5.5 ± 4.6	0.5 ± 1.0	2.2 ± 1.5	1.2 ± 1.3	0.9 ± 1.4	0.2 ± 0.5	0.6 ± 0.8
***P*-value[a]**		< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.001	0.004	0.002

[a] Independent Student's *t*-test. GEN = Group with current genital lesions; NGEN = Group without current genital lesions; DLQI = Dermatology life quality index; SD = Standard deviation

Table 4 Sexual health scores (mean ± SD) for psoriasis population

	Men				Women			
Group	**N**	**Total SQoL-M**	**N**	**Total IIEF**	**N**	**Total FSDS**	**N**	**Total FSFI**
Total [a]	278	77.2 ± 24.1	258	55.7 ± 17.2	199	11.8 ± 10.8	191	23.9 ± 9.3
GEN	110	76.1 ± 24.4	105	55.0 ± 16.9	59	16.1 ± 12.1	56	23.6 ± 8.8
NGEN	159	77.8 ± 24.1	145	56.1 ± 17.4	131	10.1 ± 9.7	125	24.2 ± 9.6
***P*-value[b]**		0.58		0.62		0.001*		0.70

[a] Individual numbers for GEN and NGEN do not add up to total numbers as patients with lacking information on the presence of current genital lesions were excluded from analysis. [b] Independent Student's *t*-test. * GEN sample mean of total FSDS score is significantly higher than NGEN comparison sample at $P = 0.001$. N = Number; SQoL-M = Sexual Quality of Life Questionnaire for use in Men; IIEF = International Index of Erectile Function; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; GEN = Group with current genital lesions; NGEN = Group without current genital lesions; SD = Standard deviation

Table 5 Possible factors associated with decline in sexual activity

	Frequency, n (%)				
Factor	**Never**	**Sometimes**	**Often**	**Always**	**Missing**
1. Psoriasis has a negative effect on physical appearance	17 (14.2)	48 (40.0)	**34 (28.3)**	**18 (15.0)**	3 (2.5)
2. Fear of partner for contagiousness	101 (84.2)	7 (5.8)	2 (1.7)	2 (1.7)	8 (6.7)
3. Fear of passing psoriasis on to children	44 (36.7)	38 (31.7)	15 (12.5)	16 (13.3)	7 (5.8)
4. Diminished sexual desire of patient	14 (11.7)	42 (35.0)	**49 (40.8)**	**14 (11.7)**	1 (0.8)
5. Diminished sexual desire of partner	51 (42.5)	34 (28.3)	20 (16.7)	5 (4.2)	10 (8.3)
6. Inconvenience by scaliness of skin	12 (10.0)	42 (35.0)	**30 (25.0)**	**35 (29.2)**	1 (0.8)
7. Inconvenience by topical therapy	20 (16.7)	41 (34.2)	**33 (27.5)**	**24 (20.0)**	2 (1.7)

Table 6 Attention given to possible sexual problems according to the patients

	Sufficient attention for possible sexual problems by heath care professional, n (%)	Wish for more frequent questioning for possible sexual problems, n (%)
Yes	44 (9.0%)	211 (43.3%)
No	132 (27.1%)	100 (20.5%)
Unknown	301 (61.8%)	165 (33.9%)
Missing	10 (2.1%)	11 (2.3%)
Total	487 (100%)	487 (100%)

Discussion

The present study shows that psoriasis has a detrimental effect on both general quality of life and sexual health. When genital lesions are present, quality of life is even worse. Sexual dysfunction and distress are particularly prominent in half of all women with psoriasis, and distress is particular high when genital skin is affected. The attention given to possible sexual problems in the psoriasis population by health care professionals is perceived by patients as insufficient.

It is known that psoriasis can have a substantial impact on health-related quality of life.[14,15,18] Our results showing that patients with genital psoriasis have a significantly worse quality of life compared with patients without genital lesions are in agreement with previous studies.[17,41] The most significant predictor of quality of life associated with psoriasis appeared to be the self-assessed psoriasis severity score (SAPASI)[42], but even when we corrected for the higher SAPASI score in the patients with genital psoriasis, this group still had a worse quality of life compared with the group without genital lesions. These findings are, to a certain extent, in accordance with the results of Schmid-Ott *et al.*[43] who found that patients with the 'sensitive' regions (lower abdomen and genitals) affected felt significantly more stigmatised and that they concealed their symptoms more often than those with other regions (both visible and invisible) affected. These feelings and concerns might have serious consequences for an individual's psychosocial well being.

Patients who had had genital psoriasis in the past had the same DLQI scores as patients who had never had genital lesions, and patients who had had genital lesions in the past had a better quality of life compared with patients with current genital lesions. This implicates amelioration in quality of life when recovering from genital psoriatic lesions. Likewise, there seems to be a trend towards improvement of the FSDS scores for women recovering from genital psoriasis.

Almost 40% of the women with psoriasis showed sexually related personal distress, which was present in the patients with genital lesions particularly. However, a significant proportion of patients without genital lesions experienced sexual distress as well. In addition, half of the women had sexual dysfunction as defined by the FSFI cutoff score, demonstrating that women with psoriasis particularly suffer from limitations in their sexual life and intimate relationships. Descriptive results from reasons for lower sexual activity after the onset of psoriasis (Table 5) further suggest that feelings of shame and embarrassment about physical appearance, scaling of the skin and topical therapy as well as reduced sexual desire might play a major role in these high distress and dysfunction scores in women. In contrast, the two groups of men showed no differences in sexual quality of life scores.

The mean SQoL-M scores incline towards normal sexual quality of life, when we compare them with the scores of 101 men who self-reported to have no problems

with their sexual function (mean ± SD: 87.13 ± 13.72).[32] Several possible factors might play a role in these gender differences: men might be less open about their sexual problems, resulting in incorrect 'normal' scores. However, the questionnaires used have been validated in Dutch men populations and showed a considerable number of men with lower scores on sexual dysfunction.[32,33] Furthermore, one might postulate that differences in sexual desire between men with psoriasis and their female partners are smaller than the differences between female patients and their male partners, making men with psoriasis less concerned about their sex life. Moreover, older women's sexual health (age ≥ 57 years; comprising a large part of our study population) appears to be more sensitive to physical health and possibly also physical appearance compared with that of older men.[44]

The results of both questionnaires regarding sexual functioning (FSFI and IIEF) indicate that sexual functioning is diminished in a large proportion of both men and women with psoriasis. Our findings correspond with other studies in small samples.[21,45] Additionally, Goulding *et al.*[46] recently published that erectile dysfunction is increased in patients with psoriasis, although psoriasis was no independent risk factor for erectile dysfunction in their study population. It is interesting that we did not find any differences in sexual function between patients with and patients without genital localisation of their psoriasis, while sexual distress was higher in women who had more affected genital skin. Apparently, localisation of the lesions at genital skin does not provoke worse sexual function in itself, but might have an impact on the subjective experience of sexual distress in women, e.g. feelings of reduced physical attractiveness because of scaling skin. This is supported by van Dorssen *et al.*[26] who state that sexual motivation and satisfaction did not correlate with localisation of the disease around the genital skin. A more recent publication denoted that the number of patients who report difficulties in sexual life seemed higher in patients with psoriatic lesions in the genital area. However, when considering several other variables of psoriasis, localisation on the genital area no longer had a significant effect on sexual life.[24]

Our finding that the older the patient at onset of genital psoriasis the worse sexual function, correlates with a recent publication on sexual function following vulvar excision, indicating that older women are at more risk for poor sexual function and quality of life following vulvar excision.[47] These findings highlight the need to distinguish differences in normal changes in sexual function with aging from those that may be attributed to the skin lesions. In addition, older women might also have more problems with coping adequately with possible sexual and intimate problems due to the psoriasis.

We showed that the attention given to possible sexual problems in patients with psoriasis is seriously insufficient. van Dorssen *et al.*[26] pleaded in 1992 for more attention to be paid to potential sexual problems in these patients, but apparently in

the meantime little has improved. Over 60% of the patients indicated that they did not know whether sufficient attention was given or not. It may be speculated that patients have never realised that doctors could also care for sexual health. In addition, it is possible that patients never made a specific demand for care regarding their sexuality, purely because they did not know what they might expect.

Among our patients almost 25% reported a decline in sexual activity since the onset of psoriasis, induced by different factors. This percentage is somewhat lower than reported in another publication, which found a decline in sexual activity in more than 40% of patients with moderate to severe psoriasis.[20] It is possible that the difference in severity of psoriasis (moderate in our group) explains this difference in percentages. Nevertheless, many patients (women in particular) indicated a negative impact of psoriasis on sexual activity and this is certainly something which medical professionals should discuss with their patients. Ideally, the physician takes the initiative to ask about quality of life and sexuality. Optionally, a very short disease-specific questionnaire such as the DLQI, which is practical and of clinical value when used in a busy clinical setting,[34] may be used. When indicated, motivated patients could be referred to a (dermato)psychologist or sexologist. For patients whose genital problems are not limited to dermatological pathology (e.g. erectile dysfunction or dyspareunia), a multidisciplinary approach with consultation of a urologist or gynaecologist is advised. We believe that better communication and counselling about (sexual) quality of life may help to improve acceptance of the skin disease and may ameliorate therapeutic results.

Limitations of our study deserve comment. A preselection bias might have been introduced because we approached a subpopulation of patients who had previously participated in research and who were all members of the Dutch Psoriasis Society. It may be hypothesised that these patients do not represent a random sample of patients with psoriasis, as they might be more interested or worried about their disease and additional (sexual) health problems. Also, respondents were younger and had more severe psoriasis compared with the nonrespondents. Given the highly intimate and personal questions it is possible that a response bias exists as particularly patients most bothered by their (genital) symptoms might have returned the questionnaires. Older patients were overrepresented, so the observed results may possibly not be extrapolated to other age groups. However, the mean DLQI scores of our study population, as well as of both separate groups (GEN and NGEN), are classified as having a 'moderate effect on patient's life' according to the manual of the DLQI. Basra *et al.*[48] recently published data which show that our mean score is within the range of the mean scores of patients with psoriasis in many other publications. Nevertheless, we used a time-modified version of the DLQI and, in consequence, the DLQI scores in the present study cannot be completely compared with existing DLQI norm scores. Unfortunately, as both male sexual health questionnaires

were developed for treatment evaluation, no cutoff scores exist for these questionnaires. Also, we were not able to compare our results with an age- and gender-matched control group. Moreover, it is possible that patients with genital lesions also had psoriatic lesions at other sensitive locations of their body which may have contributed to the worse quality of life. Nonetheless, we believe that the magnitude of our study population provides valuable insights into patient perceptions of the impact of psoriasis on quality of life and sexual function.

To conclude, in addition to quality of life, sexual health is considerably diminished in subgroups of patients with psoriasis, particularly in women who experience high levels of sexual dysfunction and, in the presence of genital lesions, also high levels of sexual distress. We underscore the need for physicians to take into account the psychosocial and sexual health when treating patients for psoriasis.

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CHAPTER

4

Patients' experience of psoriasis in the genital area

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Abstract

Background
Psoriasis in the genital area is often neglected, although it bothers a substantial number of patients.

Objective
To study both the role of the physician in the treatment of genital psoriasis and the symptom intensity of these lesions as experienced by the patients.

Methods
A detailed self-administered questionnaire (containing items on the role of the physician and genital symptom intensity, range 0–10) was filled in by members of the Dutch Psoriasis Society.

Results
Data of 277 patients with genital psoriasis were analyzed. A total of 45.8% did not discuss the presence of genital psoriasis with their physician, 25% believed that the physician paid sufficient attention to genital lesions, and 67.8% never applied treatment for genital lesions. Mean symptom intensity ranged from 2.4 to 5.1, all scores being significantly higher for women compared to men. Severe symptoms were present in up to 43.5% of patients. Of these patients, up to 38.1% did not discuss the symptoms with their physician.

Conclusion
The consultation rate for genital lesions is low, while numerous patients report a significant burden of disease.

Introduction

Psoriasis may involve all sites of the skin, including the genital area. Psoriasis in this area has long been neglected in the treatment of patients with psoriasis, whereas several reports have shown that it may represent an important problem for a substantial number of patients.[1-3] Recently, we published data on the prevalence of genital psoriasis in patients in the Netherlands. Of 1943 patients with psoriasis, over 45% reported genital presentations of psoriasis at any time during the course of their disease.[4]

It is known that healthcare professionals infrequently initiate a dialogue on sexual (dys-) function with their patients. The majority of psoriatic patients have never been asked about their sexual health by their attending doctor, and it appears that the vast majority of psoriatic patients believe that the attention for possible sexual problems is insufficient.[5-8] Likewise, the problem of genital psoriatic lesions may remain unnoticed in patients with psoriasis, whereas involvement of the genital skin may have a profound impact on quality of life and sexual health.[8]

The experience of symptoms, minor to severe, may create serious distress and may disrupt social functioning.[9] Understanding the burden of symptoms is crucial to identify a focus for intervention strategies.[9] Patients with psoriasis frequently experience physical symptoms such as skin pain and skin discomfort (e.g. itch, irritation or burning).[10,11] However, patients' experience concerning the presence and intensity of genital symptoms is only sparsely described in the current literature. Some expert opinion-based publications state that pain, pruritus and/or burning sensation, ranging from minimal to marked, may be present in patients with genital psoriasis.[12-15] However, the gold standard for the study of symptoms is based on the perception of the individual experiencing the symptom and his/her self-report.[9] One recent publication[16] denotes that there is a significant correlation between the presence of vulvar discomfort (considered as itching and/or burning) and vulvar localisation of psoriasis. The intensity of vulvar discomfort assessed according to a visual analogue scale was 3.8 (range 1–10 points). Unfortunately, the authors did not specify the intensity of different symptoms and pain was not measured at all.

General psoriatic lesions show a dynamic behaviour. Well-known deteriorating factors are stress, trauma, infections and specific medications (i.e. beta-blockers and lithium).[17] For genital psoriasis, the clinical behaviour and possible triggering factors are largely unknown.

To improve the care of patients with genital psoriasis, it is important to get an impression of the current role of the physician in the treatment of genital psoriasis. Moreover, the experience of patients regarding physical symptom characteristics of genital psoriasis (including intensity and fluctuation) will be clarified in this study. Finally, we give recommendations to optimise future care of patients with genital psoriatic lesions.

Patients and Methods

Patients and Study Design

A self-administered questionnaire was distributed to a number of members of the Dutch Psoriasis Society (n = 1579). These patients had been involved in a previous study on epidemiology of genital psoriasis[4] and had given their permission to participate in a consecutive questionnaire-based study on genital psoriasis. All patients were ≥ 18 years of age. Participants had the opportunity to consult one of the investigators by e-mail for questions regarding the study. Repeat mailings were made for unreturned surveys. A secured digital answering system was introduced to complete the questionnaire electronically. Additionally, a paper version was available for those patients who did not have internet available. Results were collected from 24 September 2009 until 31 December 2009. The answers were processed anonymously and data were linked to the corresponding answers of the preceding survey by an identification number. Medical ethics review was not required according to the local Medical Review Ethics Committee.

Questionnaires

The contents of the questionnaire regarding the previous study have formerly been described in detail.[4] The following items of that questionnaire were used for the current study: sociodemographic characteristics (age, gender and marital status) and medical data (age at onset of psoriasis, type and severity of psoriasis, current or past involvement of genital skin and age at which genital psoriasis started). The severity of psoriasis was assessed by the self-administered psoriasis area and severity index (SAPASI).[18]

The questionnaire used in the present study asked patients whether they ever experienced genital psoriasis during the course of their disease. To be able to define patients with current genital lesions and genital lesions in the past, we used the information obtained from the first questionnaire about current or past involvement. Therefore, 'current genital psoriasis' was defined as 'genital skin involved with psoriasis at least 6 months before the second questionnaire' (i.e. at the time of the first questionnaire).

If patients ever had genital psoriasis, they were asked to answer subsequent questions on their experience regarding the role of the physician involved in the care of their (genital) psoriasis (either their general practitioner or their dermatologist, gynaecologist, urologist or other physician) in this localisation of psoriasis: whether they discussed the presence of genital lesions with their physician, whether they thought that there was sufficient attention for this presentation of psoriasis and whether a biopsy was performed in the genital region to establish the diagnosis of psoriasis (by checking 'yes', 'no' or 'unknown'). In addition, we asked whether they received treatment for their genital lesions and by whom the treatment was prescribed.

Moreover, physical symptoms caused by the genital psoriatic lesions were measured. Therefore, the average intensity of itch, pain, burning sensation, scaliness, redness and induration was rated using a numeric rating scale, ('0' reflecting no symptom and '10' reflecting the worst symptom conceivable. Previously suggested ranges to explain the intensity of chronic non-malignant pain were used to classify the intensity of the physical symptoms of our interest: mild 1–3, moderate 4–6 and severe 7–10.[10]

Patients' experience concerning deterioration of genital psoriatic lesions in comparison with worsening of non-genital lesions was assessed in a multiple choice questionnaire by using an ordinal scale [classification: 'never', 'sometimes', 'often', 'always' and 'unknown']. Patients were asked which of the following items may have a possible influence on worsening of their genital psoriatic lesions: emotional stress, trauma to genital skin (e.g. during depilation), infection on genital skin (e.g. dermatomycosis), urinary infection, hormone fluctuations (e.g. menstrual cycle or pregnancy) and use of medication.

Statistical Analysis

All data were entered in a computerised database. Subsequently, statistical calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA). Data of all measured variables were checked for their distribution pattern. Continuous variables were described as medians (range) or means (± standard deviation), depending on the (non-) parametric distributions of measured variables. Discontinuous variables were described by the total frequencies and percentages of each modality. X^2 test was used to calculate the significance of differences between categorical variables; independent Student's t-test was used for differences between numerical variables. Paired samples t-test was used to calculate differences between the intensity of different symptoms. Missing values were not included in the analyses. P-values of < 0.05 were considered to be statistically significant.

Results

Baseline

An overall response rate of 31% (487 out of 1579) was achieved for our second questionnaire. All questionnaires were suitable for analysis. A total number of 210 patients never had genital psoriasis. On the other hand, 277 patients (56.9%) indicated that their genital skin had been affected by psoriasis at some time during the course of their disease. For this study, we focus on the patients who suffer(ed) from genital psoriasis (n = 277). Baseline characteristics of all these patients are reflected in Table 1.

Table 1 Patients' characteristics (N = 277)

Sex ratio		
Male	174	(62.8%)
Female	103	(37.2%)
Marital status		
Single	26	(9.4%)
Married/cohabiting	228	(82.3%)
Other[a]	23	(8.3%)
Age, years[b]	52.2	± 12.2
Type of psoriasis[c]		
Plaque	199	(71.8%)
Guttate	117	(42.2%)
Pustular	13	(4.7%)
Erythroderma	17	(6.1%)
With joint complaints	119	(43.0%)
With nail involvement	177	(63.9%)
Age at onset of psoriasis, years[b]	24.0	± 13.2
Median SAPASI score	6.9	(0-39.4)
Age at onset of genital psoriasis, years[b]	34.7	± 14.1
Current genital psoriasis		
Yes	172	(62.1%)
No	86	(31.0%)
Unknown	19	(6.9%)

SAPASI = Self-administered psoriasis area and severity index.
[a] Divorced, widowed or separated, living apart together.
[b] Mean ± standard deviation
[c] Self-reported type of psoriasis. One patient may have indicated several types of psoriasis.

The present cohort studied (n = 277) consisted of significantly more male patients (62.8%) compared to female patients (37.2%) (X^2: $P = 0.003$). The mean age of the patients at the time of the questionnaire was 52.2 (± 12.2) years and patients reported an average age at onset of genital psoriasis of 34.7 (± 14.1) years. Plaque psoriasis (n = 199, 71.8%) was the most common type of psoriasis, followed by guttate psoriasis in 117 patients (42.2%). Patients with genital psoriasis appeared to have nail involvement significantly more often (177 out of 277, 63.9%) compared to the patients without genital involvement (89 out of 210, 42.4%) (X^2: $P < 0.0001$). There was no significant difference between the presence of joint complaints between the patients with and without genital psoriasis (X^2: $P = 0.98$]

Of the 277 patients, 172 patients (66.7%) stated that they suffered from current genital lesions, and 86 patients (33.3%) had had genital lesions in the past. In 19 patients we lack information on the presence of current genital lesions.

Patients' Experience: Role of the Physician

Almost half of the patients (n = 127, 45.8%) did not discuss the presence of genital lesions with their physician; another 127 patients indicated that they discussed this issue. Age had no effect on whether or not genital lesions were discussed. Only 25.3% of all patients mentioned that their physician paid sufficient attention to their genital lesions. No significant differences were found between male and female patients for both discussion of the genital lesions and perceived attention for those lesions ($P = 0.51$ and $P = 0.20$, respectively). The vast majority of patients (92.4%) stated that a biopsy was never taken to confirm the diagnosis of genital psoriasis.

A total of 273 patients responded to the question regarding treatment of genital lesions. Over two thirds of patients (n = 185, 67.8%) responded that no treatment for their genital lesions was ever applied. Seventy out of the 88 patients who were treated for genital lesions indicated that they discussed the genital lesions with their physician. Half of the remaining 18 patients who received treatment did not discuss the presence of genital lesions with their physician, and for the other half this is unknown. In the vast majority of cases (81.4%), the treatment was prescribed by a dermatologist. Fifty-seven out of the 127 patients (44.9%) who discussed the presence of genital psoriatic lesions with their physician indicated that they did not receive any treatment.

Patients' Experience: Genital Symptoms

Table 2 shows the means and standard deviations of the genital symptom intensity scores (0–10 numeric rating scale) for the total group, the subgroup of patients with current genital psoriasis and the subgroup of patients with genital psoriasis in the past. All scores ranged between 0 and 10. Among the total group of patients, it was found that the mean intensity scores of itch, burning and pain all differed significantly (4.2 ± 2.9 vs. 3.5 ± 2.9 vs. 2.8 ± 2.7, $P < 0.0001$); thus, patients with genital psoriasis have significantly more itch than burning skin than pain. Also, the mean intensity scores of redness, scaliness and induration differed significantly (5.1 ± 2.5 vs. 3.7 ± 2.8 vs. 2.4 ± 2.6, $P < 0.0001$), meaning that patients with genital psoriasis have significantly more redness than scaliness than induration. The intensity of all symptoms was significantly higher for women compared to men ($P < 0.0001$ for all variables except for pain: $P = 0.006$). Patients with genital psoriasis in the past reported significantly lower intensity scores than patients with current genital psoriasis ($P < 0.0001$ for itch, pain, burning sensation, scaliness and redness; $P = 0.006$ for induration).

Table 3 shows that redness and itch are indicated as 'severe' in most cases and pain and induration are usually mild. Depending on the kind of symptoms, up to

Table 2 Total and subgroup scores of genital psoriasis symptom intensity (0-10 numeric rating scale)

Symptoms	Genital psoriasis			*P*-value[b]
	Total group (N = 277)[a]	Current group (N = 172)[a]	Past group (N = 86)[a]	
Itch	4.2 ± 2.9	4.8 ± 2.9	3.1 ± 2.8	< 0.0001
Pain	2.8 ± 2.7	3.2 ± 2.6	1.9 ± 2.6	< 0.0001
Burning	3.5 ± 2.9	3.9 ± 2.8	2.6 ± 2.8	< 0.0001
Scaliness	3.7 ± 2.8	4.1 ± 2.8	2.8 ± 2.4	< 0.0001
Redness	5.1 ± 2.5	5.6 ± 2.5	4.0 ± 2.3	< 0.0001
Induration	2.4 ± 2.6	2.7 ± 2.7	1.8 ± 2.2	0.006

Data are given as mean ± SD. Missing values were not included in the analysis.
[a] Number of missing responses: total group (5–12), current group (1–4), past group (4).
[b] Independent Student's *t*-test. Comparison between patients with current genital psoriasis and those with genital psoriasis in the past.

Table 3 Classification of self-reported intensity of genital symptoms

Symptoms	None (NRS: 0)	Mild (NRS: 1–3)	Moderate (NRS: 4–6)	Severe (NRS: 7–10)
Itch	16 (9.4%)	52 (30.4%)	39 (22.8%)	64 (37.4%)
Pain	37 (21.9%)	67 (39.6%)	38 (22.5%)	27 (16.0%)
Burning	32 (18.8%)	43 (25.3%)	54 (31.8%)	41 (24.1%)
Scaliness	20 (11.8%)	59 (34.9%)	46 (27.2%)	44 (26.0%)
Redness	2 (1.2%)	35 (20.6%)	59 (34.7%)	74 (43.5%)
Induration	43 (25.6%)	76 (45.2%)	28 (16.7%)	21 (12.5%)

Total numbers on which percentages are based vary because of missing data for some subjects.
NRS = Numeric rating scale

38.1% of the patients with severe genital symptoms indicated that they did not discuss the symptoms with their physician.

Patients' experience concerning deterioration of genital psoriatic lesions in comparison with worsening of non-genital lesions is diverse. The majority of patients (n = 115, 41.5%) indicated that sometimes their genital lesions worsened parallel to

their non-genital lesions. Forty-one patients (14.8%) answered 'never', 46 patients (16.6%) 'often' and 40 patients (14.4%) 'unknown' to this particular query.

Patients attributed emotional stress most frequently to worsening of genital lesions (n = 194, 70.0%). Trauma to genital skin, infection on genital skin and hormone fluctuations may affect progression of genital lesions according to 15.9, 10.5 and 8.7% of patients, respectively. Urinary infection and the use of medication (NSAIDs, beta-blockers or others) were indicated as deteriorating factors only by 2.5 and 4.3% of patients, respectively.

Discussion

This exploratory study provides insight into the experience of patients with genital psoriasis. Almost half of the patients did not discuss the presence of genital lesions with their physician, and over two thirds of the patients never received treatment for these lesions. A comprehensive outline of the genital symptom intensity and fluctuation was provided.

A remarkably large group of patients (45.8%) did not discuss genital psoriasis symptoms with their physician. Among these patients, even 20–40% are classified as having 'severe' symptoms. No differences between men and women were found. It is possible that patients may have fear or shyness for genital examination and that they are therefore reluctant in starting the conversation about their complaints. Unfortunately, we do not know who initiated the dialogue in the cases who did discuss the genital symptoms. However, we think that it is justified to advocate a more proactive approach of possible genital psoriasis in general practice.

A noteworthy number of patients indicated that they never received treatment for their genital lesions. Within this group there are patients who did not discuss the presence of the lesions with their physician, but also a significant proportion of patients who actually did discuss their complaints. This finding may be attributed to the fact that during busy outpatient consulting hours, attention is focused on non-genital skin and that genital complaints are being overlooked.

A number of patients stated that they did not discuss the symptoms, but did receive treatment. Therefore, it is very likely that a considerable number of patients practice self-treatment, which is an unfavourable situation since the genital skin has a high sensitivity and there might be an increased penetration of topical treatment modalities in the genital area. Otherwise, it is also possible that patients are treated with systemic medication which certainly may have beneficial effects on genital psoriatic lesions while not necessarily prescribed for those particular lesions.[19]

At least 80% of the patients studied in this investigation reported genital sensory skin symptoms (itch, pain or burning sensation), which corresponds with findings in

another publication on skin pain and discomfort in non-genital psoriasis.[10] Sampogna et al. published somewhat lower percentages; however, their numbers might be underestimated as only patients who reported symptoms 'often' or 'all the time' were counted.[11] For all symptoms, patients reported mean genital intensity scores in the mild to moderate range, which is equivalent to pain and discomfort intensity scores in non-genital psoriasis.[10] Zamirska et al. also found mild to moderate vulvar symptoms in their population of psoriatic women with vulvar discomfort ($n = 41$). Only 22 patients in that study had psoriatic lesions on the vulva.[16]

It is known that psoriatic patients with pain experience significantly more often and more severe interference with function compared to patients with skin discomfort.[10] We did not investigate to what extent different genital symptoms interfered with daily functioning. Nevertheless, we do know that our patients experience a considerable impact on quality of life and on sexual health.[8] Besides, it is known that in patients with vulvar lichen sclerosus, which like psoriasis is clinically characterised by itching and burning and has also a chronic nature, there is a correlation between the intensity and/or frequency of vulvar symptoms (pain, burning, itching, dryness) and a poorer quality of life.[20] Also, patients with vulvar lichen sclerosus who experience more itch and/or pain report more sexual distress and more problems regarding several dimensions of sexual functioning.[21]

Interestingly, all reported symptoms were more severe in women than in men, which is also found in other publications on non-genital psoriasis.[11,22] When we speculate, this finding may reflect biological or psychological differences between both genders (women have different pain perception or pain threshold and tolerance levels compared to men and maybe this is also the case for other symptoms measured in our investigation).[23,24] Besides, maybe women are less aggressively treated for their genital psoriasis than men.

It is remarkable that patients with current genital psoriasis reported significantly more intense symptoms compared to patients with genital psoriasis in the past. Possibly, patients might forget symptom intensity when genital lesions have resolved.

We found no relationship between the deterioration of genital psoriatic lesions and worsening of non-genital lesions. This may possibly be due to variance in applying treatment to the different skin regions (treating non-genital lesions and not treating genital lesions).

A very large group of patients indicated stress as aggravating factor for their genital lesions. If stress causes worsening of genital psoriasis, then a vicious circle is easily created: stress worsens genital psoriasis, which in itself creates a large amount of distress.[8] We think that starting a dialogue about possible genital complaints and (multidisciplinary) treatment of these lesions may relatively easily break through this circle.

This study, with an overall response rate of 31%, has uncovered several important findings. However, we acknowledge certain limitations of our study. The population studied may possibly not reflect a random sample of psoriatic patients, as only patients who previously participated in research and who are all members of the Dutch Psoriasis Society were included. These patients may be more bothered by their genital symptoms compared to the general psoriatic population. Besides, we were not able to compare our results with an age- and gender-matched control group with genital disease different from psoriasis. Also, male patients predominated in this investigation. This is a logical consequence of the fact that the present cohort is a selection of the respondents to our second questionnaire. Significantly more male patients responded to that questionnaire.[8] Moreover, in the study population of the first questionnaire, significantly more male patients compared to female patients reported genital psoriasis.[4] Also, the retrospective design of this study might have caused a recall bias, which may have resulted in an over- or underestimation of the calculated results, e.g. the difference between symptom intensity in patients with current genital psoriasis and those with genital psoriasis in the past. We are aware of the multiple differential diagnoses for genital psoriasis, and although we deliberately asked for the presence of 'psoriatic lesions at the genital skin', it is insuperable that in this questionnaire-based study some inaccurate cases have been included. Despite these possible biases, the current study is the first describing subjective patients' experience regarding the role of the physician and genital psoriasis symptoms of a large number of patients.

The consultation rate for genital psoriasis lesions is low, while numerous patients report a significant burden of disease. We recommend a proactive and patient-centred approach to identify and treat patients with genital psoriasis. Based on the results of this investigation, we started a specialised outpatient clinic for patients with genital psoriasis. The future will learn whether this approach, with focus on treatment and improvement of (sexual) quality of life, contributes to the well-being of patients with psoriasis.

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CHAPTER

5

Genital psoriasis awareness program: Physical and psychological care for patients with genital psoriasis

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Abstract

Genital psoriasis is a neglected manifestation of psoriasis, although it affects numerous patients and has impressive effects on (sexual) quality of life ((S)QoL). We aimed to assess the value of specialised care for patients with genital psoriasis. Patients were treated for at least one year at a specialised research outpatient clinic with extensive attention for genital lesions and (S)QoL. The genital lesions were treated according to a stepwise algorithm. First follow-up was planned after six weeks; subsequent follow-up visits were scheduled basically every three months. At every visit, psoriasis severity and (S)QoL were measured with validated tools. Differences in scores between visits were analysed by a mixed model for repeated measures. Forty-two patients were included (M:F = 25:17). All objective and subjective genital psoriasis severity and QoL parameters improved significantly within the first follow-up period of approximately six weeks. In female patients, sexual QoL also significantly improved. In conclusion, genital psoriasis can relatively easy be treated within limited time exposure, resulting in significant improvement of QoL. Prompt and simple adjustments in the provided care are enough to accomplish this.

Introduction

Psoriasis in the genital area is a rather neglected manifestation of psoriasis. However, the number of patients affected with genital psoriasis is considerable. Several studies show that involvement of the genital skin occurs in 29-46% of psoriasis patients sometime during the course of the disease.[1-6]

Most patients with genital psoriasis experience localised mild to moderate sensory skin symptoms such as itch, pain and/or burning.[7-10] Diagnosis of genital psoriasis can usually be made on the basis of its typical clinical appearance that includes symmetrical, well-demarcated, brightly erythematous thin plaques that usually lack the typical dry scaling.[11] Sometimes, evident scaling is seen on the more keratinising regions of the genital skin and lesions may be accompanied by painful rhagades or fissures.[12-15]

Patients with genital psoriasis have significantly worse quality of life (QoL) scores compared with patients without genital lesions.[16-18] In addition, numerous patients with psoriasis have sexual dysfunction.[16,19,20] Out of all patients with psoriasis, 25 – 40% report a decline of sexual activity since the onset of psoriasis, mainly due to diminished sexual desire, embarrassment of physical appearance and inconvenience caused by scaliness of the skin or topical therapy.[16,21] Particularly in women, there is evidently more sexual distress and probably also sexual dysfunction when genital skin is affected.[16,22]

Treatment of genital lesions is challenging, as the genital skin is thin and sensitive. Based on a systematic literature review about this topic, there is room for mild to moderate potent corticosteroids, possibly combined with vitamin D analogues or tar-based treatment.[11] A third-line treatment option is the use of an immunomodulator, although evidence is still scarce. Systemic treatment is generally not used solely for genital psoriasis[11]; however, when prescribed it can also improve genital lesions.[23,24]

Genital lesions and the accompanying deterioration of (sexual) QoL ((S)QoL) are seldom subject of discussion at the outpatient clinic.[1,25] An earlier study showed that less than 10% of the patients believe that sufficient attention is given to sexual problems by their doctors, while many patients believe that it would have been beneficial to have received more care in this area.[16,26] A possible explanation for this incongruence is that patients might be uncomfortable about or unaware of the possibility of discussing sexual problems with their clinicians.[27]

It is clear that there is room for improvement in physical and psychological care for patients with genital psoriasis. Therefore, a research outpatient clinic with extensive attention for (S)QoL and topical therapy for patients with genital psoriasis was introduced. Based on the data collected from this clinic, this study will provide an overview of the changes in disease severity and (S)QoL parameters during follow-up. Additionally, results of the evaluation of the clinic by the patients after follow-up are presented.

Methods

Study population

Patients with psoriasis and genital symptoms who participated in a previous questionnaire-based study on (S)QoL in patients with genital psoriasis[16] or who visited the regular dermatology outpatient clinic of the Radboud university medical center were invited during March 2010 and October 2011 to visit our research outpatient clinic.

Patients were included for follow-up when they had clinically (confirmed by a dermatologist) or histopathologically confirmed genital psoriasis, were aged over 18 years and consented to participation. According to the local Medical Research Ethics Committee, medical ethical review was not required for this study.

Study design

We conducted a cohort study between March 2010 and September 2012. Patients were assessed for eligibility at baseline and, when included, followed for at least one year. The first follow-up visit (V1) was planned 6 weeks after baseline visit. Further follow-up visits were basically scheduled every 3 months during one year. However, the schedule was intensified when medically needed (i.e. when treatment was adjusted). Also, when patients did not comply with the exact scheme, data were taken into account. All patients were followed and all data were collected by one of the clinical investigators (KM).

At every visit, measurements determining psoriasis severity and (S)QoL were completed. In case of possible sexual dysfunction or impaired QoL, patients were offered referral to a sexologist or (dermato-)psychologist.

After completing follow-up, patients were requested to evaluate the care offered at the outpatient clinic by filling in an anonymous evaluation form. This form contained questions about change of physical complaints during follow-up, attention for (S)QoL at the outpatient clinic and the overall benefit from visiting the outpatient clinic.

Treatment algorithm

At baseline, topical therapy was selected according to a stepwise treatment algorithm, which we published in 2011.[11] An overview of the prescribed treatments is shown in Table I. Additionally, the daily use of an emollient was advised to all patients. When the patient was already effectively treating the genital psoriasis with treatment comparable to our algorithm, this was continued. When, according to the clinical investigator, at follow-up there was insufficient clinical improvement in spite of compliance we prescribed the next step in the algorithm.

We considered the use of systemic medication for non-genital psoriatic lesions relevant when started during the study period and duration was sufficient to have possible systemic effects on genital lesions.

Table I Treatment algorithm and overview of prescribed therapy for genital psoriasis

Step	Modality	Intensity	Frequency (per day)	Patients (N)	Remarks
1	Mild potent corticosteroid cream	Two weeks daily, then intermittent: 4 days/week	Once	16	
2	Mild potent corticosteroid cream + Vitamin D analogue ointment	Intermittent: 4 days/week Daily	Once Twice	18	N = 5 started mild corticosteroid cream concurrently with vitamin D analogue ointment
3	Moderate potent corticosteroid cream Followed by: Mild potent corticosteroid cream + Vitamin D analogue ointment	Two weeks daily, then two weeks intermittent: 4 days/week Intermittent: 4 days/week Daily	Once Once Twice	5	N = 2 started short-term higher potent corticosteroid cream before step 1 & 2 because of severe lesions N = 1 used mild corticosteroid cream before inclusion, Vitamin D ointment and higher potent steroid cream were added during the study.
4	Calcineurin inhibitor cream (whether or not combined with mild potent corticosteroid cream)	Two weeks daily Then tempered to intermittent Intermittent: 4 days/week	Twice Once Once	0	
5	Coal tar cream + Mild potent corticosteroid cream	Daily Intermittent: 4 days/week	Twice Once	0	
Other				3	N = 2 Daily tacrolimus ointment at baseline, addition of mild potent corticosteroid cream N = 1 Alternating mild and higher potent corticosteroid cream

Outcome measures

Psoriasis severity and (S)QoL assessments were conducted at baseline and every follow-up visit (see Table II and Appendix).

Statistical analysis

All data were stored in an electronic database and statistical analysis was performed using IBM SPSS Statistics 20. Data for all included patients were analysed. Two-sided *P*-values < 0.05 were considered significant. Continuous variables were presented as median (range) or mean ±SD, depending on their distribution pattern. Categorical variables were summarised by counts and percentages. Missing values were processed as described for the different scoring systems. For other variables, missing data remained missing.

Differences between men and women at baseline were tested with Students' *t*-test or Mann-Whitney *U* test. The association between variables was evaluated with Spearman's or Pearson's (two-tailed) correlation coefficient, depending on the distribution of the data.

The course of psoriasis severity and (S)QoL during the study period was modelled with a restricted maximum likelihood-based linear mixed model for repeated measures, using an autoregressive correlation structure with lag 1 and custom hypothesis testing. This model corrects for missing data and variation in follow-up interval. Skewed variables were log transformed before analysis. In order to evaluate whether psoriasis severity and (S)QoL improved after the baseline visit, mean scores of variables during the total follow-up period were compared to scores at baseline. In order to evaluate whether there was additional improvement after V1, mean scores of variables at follow-up visits 2-6 were compared with V1. In a similar way, we evaluated whether there were additional benefits in the treatment period between follow-up visit 2 and follow-up visits 3-6.

Results

Baseline characteristics

Fifty-one patients who visited the outpatient clinic were screened for inclusion. Nine patients appeared to have other diagnoses than genital psoriasis (eczema $n = 3$, lichen sclerosus $n = 1$, lichen simplex $n = 1$, unspecified $n = 1$) or had no visible skin lesions and had no previous diagnosis of genital psoriasis ($n = 3$) and were therefore excluded. As a result, data of 42 patients were eligible for inclusion. Characteristics of these patients are depicted in Table III.

The median interval between baseline and V1 was 6 weeks (range 4-24 weeks) and the median interval between the follow-up visits was 13 weeks (range 4-43

Table II Psoriasis severity and (sexual) quality of life outcome measures

Psoriasis severity	Name	Description	Range	Interpretation
Objective	BSA	Overall psoriasis coverage	0 - 100%	↑ score = ↑ severity
	PASI	Overall psoriasis severity	0 - 72	↑ score = ↑ severity
	IA	Genital psoriasis coverage	*Not applicable*	↑ score = ↑ severity
	SUM	Genital psoriasis severity	0 - 12	↑ score = ↑ severity
	IGA	Genital psoriasis severity	None (0) - very severe (5)	Accordingly
Subjective	PGA	Genital psoriasis severity	None (0) - severe (4)	Accordingly
	VAS - itch	Severity of genital itching	0 - 100	↑ score = ↑ severity
	VAS - pain	Severity of genital pain	0 - 100	↑ score = ↑ severity
	VAS - burning	Severity of genital burning	0 - 100	↑ score = ↑ severity
QoL				
General	EQ-5D index	General health-related QoL	0 - 1	↑ score = ↑ QoL
	EQ-VAS	General QoL	0 - 100	↑ score = ↑ QoL
	DLQI	Dermatology specific QoL	0 - 30	↑ score = ↓ QoL
Sexual	FSDS	Female sexual distress	0 - 48	↑ score = ↓ SQoL
	SQoL-M	Sexual QoL for men	0 - 100	↑ score = ↑ SQoL

BSA = Body surface area; PASI = Psoriasis area and severity index; IA = Investigators assessment of affected genital skin in cm^2; SUM = Sum of severity score for erythema, desquamation and induration; IGA = Investigators global assessment; PGA = Patient global assessment; VAS = Visual analogue scale; QoL = quality of life; EQ-5D index = 5-Dimension European QoL - index-score; EQ-VAS = 5-Dimension European QoL - visual analogue scale; DLQI = Dermatological life quality index; FSDS; = Female sexual distress scale; SQoL-M = Sexual QoL questionnaire for use in men

Table III Baseline characteristics

	N	(%)
Inclusion	42	
Men	25	(60)
Women	17	(40)
Clinically confirmed	41	(98)
Histologically confirmed	1	(2)
Cigarette use		
- Current smoker	17	(40)
- Never smoker	14	(33)
- Former smoker	11	(26)
Therapy for genital psoriasis at baseline	30	(71)
- Mild potent CS	6	
- Low potent CS	10	
- Moderate - high potent CS	2	
- Vitamin D analogue	3	
- Emollient	3	
- Other	6	
Age at inclusion (Years, mean ± SD)	50.1	±13.7
Age at diagnosis psoriasis (Years, mean ± SD)	29.4	±17.4
Duration of psoriasis (Years, mean ± SD)	20.7	±14.0
Age at diagnosis genital psoriasis (Years, mean ± SD)	40.7	±15.1
Duration of genital psoriasis (Years, median, range)	7.7	0.7 – 52.2

N = Number; SD = Standard deviation; CS = Corticosteroid

weeks). Patients had a median number of 5 follow-up visits. Two patients were lost to follow-up before V1.

The cohort consisted of 25 (60%) men and 17 (40%) women. Mean age at inclusion was 50 years, ranged between 20 and 80 years and was similar for both genders. Patients had a mean ±SD age of 40.7 ±15.1 at diagnosis of genital psoriasis and the median duration of genital psoriasis was 7.7 years, range 0.7 - 52.2 years. In addition to genital psoriasis, 22 patients (55%) had also perianal psoriatic lesions; men and women were equally affected.

Thirty patients (71%) were using therapy for genital psoriasis at baseline; six were treated with mild potent corticosteroid cream, in accordance with our protocol. The remaining 24 patients used either too potent (n = 10) or too mild (n = 2) corticosteroids, solely vitamin D analogues (n = 3) or emollients (n = 3). Six patients received other therapies such as coal tar ointment with precipitated sulphur, mild potent

corticosteroid cream combined with either silver sulfadiazine or fucidic acid cream and calcineurin inhibitor cream whether or not combined with fucidic acid cream.

During the study, all 42 patients received topical therapy for their genital psoriasis, see Table I. The vast majority of patients (n = 34, 81%) showed adequate improvement with the use of a mild potent corticosteroid cream with or without the addition of Vitamin D analogue ointment. Two of those patients were also prescribed 5% or 10% salicylic acid because of substantial desquamation of keratinised skin. Higher potent corticosteroid cream was prescribed in 5 patients. Two of them started with this high potent therapy followed by milder corticosteroid and Vitamin D analogue, because of the severity of genital lesions at baseline visit. Three patients used other topical therapies.

Eight patients used relevant systemic therapy for their non-genital psoriasis during the study: UVB (n = 5), methotrexate (n = 2) and fumaric acid (n = 1). In addition to treatment at the research outpatient clinic, one patient was referred to a sexologist and six patients consulted a dermato-psychologist.

Psoriasis severity and (sexual) quality of life

Psoriasis severity and (S)QoL data at baseline are summarised in Table IV. Severity of psoriasis in general was moderate (PASI 5.7, SD 4.1). There were no significant differences between men and women concerning baseline scores of psoriasis severity and (dermatological) QoL.

The investigator classified the severity of genital psoriasis as mild to moderate in the vast majority of patients (n = 29, 69%) (Investigators Global Assessment (IGA): mean 2.5). Most patients (n = 24, 57%) experienced the genital psoriasis as being (very) mild (Patient Global Assessment (PGA): mean 2.2). Two patients had no visible lesions at baseline. IGA and PGA showed to be moderately correlated (r = 0.50, P = 0.001).

Median EQ-5D index and average EQ-VAS were 0.84 (similar to age matched norm score of general population)[28] and 72.7 (slightly lower than age matched general population)[28], respectively. Mean DLQI score was 9.1, indicating a moderate adverse effect on patient's life.[29] EQ-5D index and DLQI showed a very weak negative association at baseline (r = -0.3, P = 0.060). Patients had mean scores for sexual QoL of 22.8 (Female Sexual Distress Scale [FSDS]) and 70.7 (SQoL Questionnaire for use in Men [SQoL-M]). There was hardly any association between the duration of genital psoriasis and sexual QoL (FSDS: r = 0.06, P = 0.844. SQoL-M: r = 0.39, P = 0.056). Eight of the thirteen women with baseline FSDS data (62%) were identified as having sexually-related personal distress. No cut-off values are available for the SQoL-M.

Follow-up data

As shown in Table IV, a significant improvement in all variables, except for EQ-VAS and SQoL-M was obtained between the baseline visit and V1. For all variables, except for BSA, VAS Itch, DLQI and FSDS no further significant changes were found after V1.

Table IV Psoriasis severity and (sexual) QoL: baseline data and effect during follow-up

Variable	Baseline value[a]	V1 vs. Baseline		V2-6 vs. V1		V3-6 vs. V2	
		Mean (95% CI)	*P*-value	Mean (95% CI)	P-value	Mean (95% CI)	*P*-value
BSA [b]	3.9 (0.2 – 56.5)	**-58% (-75%, -29%)**	**0.001**	**-44% (-67%, -6%)**	**0.030**	-24% (-56%, 31%)	0.318
PASI	5.7 ± 4.1	**-1.5 (-2.6, -0.5)**	**0.004**	-0.4 (-1.4, 0.7)	0.502		
IA	38.0 ± 40.2	**-17.6 (-29.9, -5.4)**	**0.005**	2.3 (-10.3, 15.0)	0.717		
SUM	4.3 ± 2.0	**-1.6 (-2.3, -0.8)**	**<0.001**	0.0 (-0.8, 0.7)	0.941		
IGA	2.5 ± 1.0	**-1.2 (-1.5, -0.8)**	**<0.001**	-0.2 (-0.6, 0.1)	0.213		
PGA	2.2 ± 1.2	**-0.9 (-1.3, -0.5)**	**<0.001**	0.0 (-0.4, 0.4)	0.934		
VAS Itch	56.1 ± 28.2	**-30.9 (-40.0, -21.7)**	**<0.001**	**-11.1 (-20.2, -1.9)**	**0.018**	0.4 (-9.2, 10.0)	0.937
VAS Pain	35.8 ± 31.8	**-21.5 (-30.1, -12.8)**	**<0.001**	-7.5 (-16.3, 1.3)	0.094		
VAS Burning	40.0 ± 30.7	**-19.2 (-28.9, -9.5)**	**<0.001**	-6.0 (-16.0, 4.0)	0.238		
EQ-5D index [b]	0.84 (0.01 – 1.00)	**20% (2%, 40%)**	**0.024**	2% (-14%, 20%)	0.853		
EQ-VAS	72.7 ± 18.3	5.2 (-0.30, 10.7)	0.064	1.6 (-4.1, 7.3)	0.585		
DLQI	9.1 ± 8.1	**-5.0 (-6.9, -3.0)**	**< 0.001**	**-2.2 (-4.2, -0.2)**	**0.030**	-1.5 (-3.6, 0.5)	0.137
FSDS	22.8 ± 16.2	**-14.7 (-20.3, -9.0)**	**< 0.001**	**-8.1 (-13.5, -2.7)**	**0.004**	-5.4 (-10.8, 0.1)	0.054
SQoL-M	70.7 ± 31.6	5.5 (-4.3, 15.3)	0.270	4.1 (-5.9, 14.1)	0.420		

[a] = Data are given as mean (± standard deviation) or median (range); [b] = Log transformed data; effects in percentages; Two-tailed *P*-value < 0.05, statistically significant improvement of variable is shown in bold. V1 = First follow-up visit; V2-6 = Second – sixth follow-up visit; CI = Confidence interval; BSA = Body surface area; PASI = Psoriasis area and severity index; IA = Investigators assessment of affected genital skin in cm^2; SUM = Sum of severity score for erythema, desquamation and induration; IGA = Investigators global assessment; PGA = Patient global assessment; VAS = Visual analogue scale; EQ-5D index = 5-Dimension European QoL - index-score; EQ-VAS = 5-Dimension European QoL - visual analogue scale; DLQI = Dermatological life quality index; FSDS = Female sexual distress scale; SQoL-M = Sexual QoL questionnaire for use in men.

Scores of BSA, VAS Itch (Fig. 1), DLQI and FSDS showed also significant changes after V1 with no further significant changes after V2. Women showed significant improvement on more parameters (BSA, PASI, IA, SUM, IGA, PGA, VAS Itch, VAS Pain, VAS Burning, DLQI and FSDS) compared to men (BSA, IA, SUM, IGA, VAS Itch, DLQI) (detailed data not shown).

Of all included patients, 27 (mean age 54.4 years; 18 men, 9 women) filled in the evaluation form regarding their visits to the research outpatient clinic. Sixteen patients (59%) experienced an improvement of their complaints, eight (30%) remained stable and three (11%) reported deterioration of genital psoriasis. All 27 patients rated the attention for QoL as sufficient. Twenty-four patients gave their opinion about the attention for sexual QoL: 22/24 (92%) defined this as sufficient. Of the 24 patients who answered the question, 22 (92%) indicated that they benefitted from visiting the research outpatient clinic.

Figure 1 Visual analogue scale (VAS) itch during follow-up

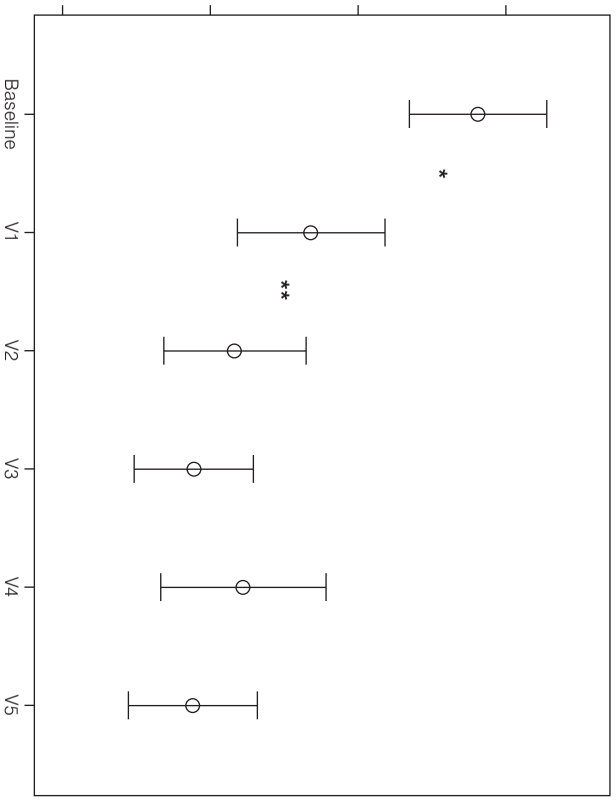

Illustration of mean VAS Itch (95% CI) scores during follow-up. Significant improvement between Baseline and first follow-up visit (V1)* and between V1 and second-sixth follow-up visit (V2-6)**. V6 is not shown because of extensive confidence interval (CI).

Discussion

This unique cohort study following patients with genital psoriasis who visited a research outpatient clinic focusing on care for genital psoriasis and possible additional psycho-sexual effects provided new insights in the value of such specialised care. Objective and subjective genital psoriasis severity and QoL significantly improved within the first follow-up period of approximately six weeks. In female patients, sexual QoL also significantly improved. Furthermore, the majority of patients highly appreciated this specialised care.

The studied cohort, consisting of patients with a diagnosis of genital psoriasis, had moderate to severe psoriasis in general and mild to moderate genital lesions. Dermatological QoL was moderately affected, as shown by the mean DLQI score of 9.1.[29] Besides, sexual QoL was highly devastated in female patients (over 60% of the patients were classified as having distress; mean FSDS was 22.8). In men, the SQoL-M data (mean 70.7) indicated slightly diminished sexual QoL when compared to the normal value of 87.1.[30] These findings are in accordance with prior studies. Indeed, involvement of genital skin in patients with psoriasis is one of the situations that lead to a significantly impaired (S)QoL despite relatively mild psoriasis severity scores. [16,31] Particularly in women with genital psoriasis, sexual distress is higher and sexual function is more significantly impaired compared to those without genital lesions.[16,22] These findings are confirmed in several other studies that show an impact of (genital) psoriasis on sexual function in 30-70% of patients with psoriasis.[21,32-35]

It is interesting that both the objective and subjective severity of genital psoriasis as well as DLQI-scores show significant and clinically relevant improvement between baseline and V1 after approximately six weeks, when topical therapy for genital lesions is prescribed and attention is given to problems causing (sexual) dysfunction. Women showed improvement on more parameters than men. However, significant improvement on several disease severity and QoL parameters was seen in both genders. It should be remarked that study groups in this gender specific analysis were small and that analysis therefore may not have shown significant improvement for some variables in men. For most parameters a plateau was reached already after V1 (six weeks interval). BSA, VAS itch, DLQI and FSDS improved even further, up to the second follow-up visit at 19 weeks, after which a plateau was reached. In women, sexual QoL improved, while in men it did not improve notably. An explanation for this may be that the sexual QoL in men was not severely enough affected, so there was less room for improvement.

The fact that clinical improvement has a substantial beneficial effect on sexual life and that time dedicated to explanation of disease as well as treatment support is associated with improved QoL in a very short time was described before.[33,36] These findings suggest a need for attention for possible genital psoriasis during the first consultation in daily clinical practice. It is also worthwhile to invest time and promptly address sensitive issues like impact on QoL and sexual health as this can have major and rapid beneficial effects for psoriasis patients.

There might be a role for a dedicated nurse practitioner in the care for patients with (genital) psoriasis focusing on education, treatment support and psychosocial needs.[36,37] It is proven that visiting a dedicated, multidisciplinary clinic is associated with an improvement in QoL.[38] Therefore, a multidisciplinary, well-trained health care team of a dermatologist collaborating with a gynaecologist, urologist, (dermato-) psychologist or sexologist would be of excellent value for the comprehensive management of genital psoriasis and its implications.

Eight patients used relevant systemic medication for their non-genital psoriasis, which may have biased the study outcomes we presented. However, analysis without those patients, showed roughly similar effects during follow-up. It can be stated that whether or not treated with systemic psoriatic medication, genital psoriasis severity, disease-specific QoL and female sexual health significantly improve within the first follow-up period with focusing on care for genital psoriasis and its possible additional psycho-sexual effects.

The average baseline EQ-5D index value was similar to that of the age-matched general population[28]. Nevertheless, improvement of this value was seen during follow-up. However, there appeared to be one patient with a very influential outlying EQ-5D index value at baseline, which affected the outcome of the follow-up data. Remarkably, when excluding this patient from analysis, EQ-5D index showed no significant improvement during follow-up. Also, there was only a slight association between EQ-5D index and DLQI. Considering these findings, the EQ-5D index and DLQI obviously capture different aspects of health-related QoL, which was also concluded by Nordin et al.[39] We agree with their hypothesis that the DLQI may be more sensitive to detect change in QoL of psoriasis patients, as the DLQI is dermatology specific whereas the EQ-5D measures health-related QoL for health-economic analyses. Additionally, sexual health is completely missing in the EQ-5D measurement, notwithstanding the fact that it is frequently affected in psoriasis patients. It is important to realise the purpose of using a health measurement tool, avoiding that such a tool is randomly selected.

Although this study reveals a number of interesting points regarding the care for patients with genital psoriasis, certain limitations have to be acknowledged. As patients were members of the Dutch Psoriasis Society or visited a tertiary care facility, it may be argued that the study population does not represent a random sample of psoriasis patients. It is also possible that response bias i.e. wanting to meet the expectations of the researcher influenced the answers given by patients to some extent. Besides, we acknowledge that life events and the natural course of psoriasis may have influenced the outcome. As blinding was not feasible, observer bias could

have influenced the severity scores. Only a limited number of patients participated in this study. Nevertheless, the significant results found in the current small study group are supportive for the validity of our findings. The introduction of a control group would have provided more insight in the real value of intensified care compared to standard daily clinical practice. However, it is hardly possible to monitor daily clinical care for genital psoriasis without the awareness of patients and physicians of being studied.

To conclude, this study showed that genital psoriasis, though devastating for QoL and (particularly in women) for sexual health, can be treated relatively easy within limited time exposure. Prompt and simple adjustments in the provided care are enough to accomplish this. Routine attention for possible genital psoriasis and accompanying impact on (S)QoL is imperative. Therefore, we highlight the need for well-trained and motivated clinicians.

Appendix: outcome measures

Psoriasis severity

We used the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA) to score the clinical severity of psoriasis in general. PASI assesses the severity of psoriasis on a scale ranging from 0 (no psoriasis) to 72 (severe psoriasis)[40] and BSA describes the percentage of surface skin affected by psoriasis ranging from 0 to 100%.

The clinical severity of genital psoriasis was assessed by the Investigators Global Assessment (IGA), SUM score and the Investigators Assessment of the extent of genital psoriasis (IA: surface of affected genital skin in cm^2). The IGA-score is depending on whether genital psoriasis is cleared (0), minimal (1), mild (2), moderate (3), severe (4) or very severe (5). The SUM score of genital psoriasis is calculated as the sum of the severity scores for erythema, desquamation and induration using the scoring system from the PASI (range 0-4 per item). The total SUM score ranges between 0 (no lesions) and 12 (very severe lesions).

Severity of genital psoriasis as experienced by the patient was measured by the Patient Global Assessment (PGA) ranging between clear (0) and severe (4), and Visual Analogue Scales (VAS) on itch, pain and burning of genital skin (range 0-100).

(Sexual) quality of life

The 5-Dimension European QoL (EQ-5D) health survey was used to measure generic QoL. This survey has two parts. The first part assigns an index-score for the self-reported health state, including five domains. This index-score ranges between 0 and 1, where 0 represents death and 1 represents perfect health. Total scores were calculated by using the Dutch EQ-5D Tariff.[41] When responses were missing for one or more of the domains, index scores were not calculated. The second part is a VAS, ranging between 0 (worst imaginable health state) and 100 (best imaginable health state).

The Dermatology Life Quality Index (DLQI) was used to assess the extent of the effect of psoriasis on daily living, with overall scores ranging from 0 (‘not at all’) to 30 (‘very much’). In case of missing data, scores were calculated according to the manual.[29]

Sexual QoL in female patients was measured by the Female Sexual Distress Scale (FSDS).[42] The total scores range from 0 to 48, with higher scores corresponding to higher levels of sexual distress. A score of ≥ 15 is the recommended cut-off value to establish the presence of sexually related personal distress. With more than 10% of answers missing, questionnaires were excluded. The Sexual QoL Questionnaire for use in Men (SQoL-M) measures sexual QoL in men. Total scores range from 0 to 100, with higher scores corresponding with a better sexual QoL.[30] According to the manual, with over 50% missing answers, the questionnaire was excluded from analysis.

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PART

B

CHAPTER

6

Skin cancer and (pre)malignancies of the female genital tract in renal transplant recipients

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Abstract

Immunosuppressive therapy in renal transplant recipients (RTR) is associated with an increased risk for the development of (pre)malignancies involving the skin and the female lower genital tract. We assessed whether yearly cervical screening was performed and evaluated the development of skin cancer and gynaecological (pre) malignancies in RTRs. Female RTRs (n = 224), transplanted between 1991 and 1995, were analysed retrospectively. Sociodemographic patient characteristics, frequency and results of cervical smears and prevalence of cutaneous, cervical, vaginal or vulvar (pre)malignancies were investigated and compared with that in the general population. A mean of 0.2 cervical smears per patient per year was found to have been performed in RTRs, which is significantly less than the recommended screening ratio of 1.0 for female RTRs ($P < 0.001$). The risk for RTRs to develop malignancies of the female lower genital tract was increased: twofold to sixfold for cervical intraepithelial neoplasia, threefold for cervical carcinoma and 50-fold for vulvar carcinoma. Cervical screening is not performed in accordance with the advised yearly intervals, and the risk for RTRs to develop vulvar and cervical (pre)malignancies is increased. More attention should be paid to the vulvar and cervical surveillance of RTRs by both medical specialists and general physicians.

Introduction

Each year, more than 800 renal transplantations (RT) are performed in the Netherlands according to the Netherlands Organ Transplantation Registration (NOTR). Solid organ transplantation requires the administration of lifelong intense immunosuppressive therapy. The strategies to reduce graft rejection have improved considerably since the first successful kidney transplantation in 1954.[1,2] At present, most immunosuppressive regimens combine a calcineurin inhibitor (ciclosporin or tacrolimus) with an adjunctive agent (azathioprine, mycophenolate mofetil or sirolimus) and corticosteroids, resulting in a remarkable increase of patient survival.[2] The current immunosuppressive regimes have led to a 1-year patient and graft survival of more than 90% and the incidence of acute rejection has fallen to 10–15%.[2] This high survival rate has made it incumbent on the medical specialists to pay increasing attention to the long-term side-effects of immunosuppressive medication.

It is known that renal transplant recipients (RTRs) have at least a threefold to fivefold increase of risk to develop any kind of cancer compared with the general population.[1,3-5] The relative risk with respect to specific cancers, such as skin cancer, post-transplant lymphoproliferative disorders, Kaposi's sarcoma and human papilloma-virus (HPV)-related malignancies of the lower genital tract e.g. cervix, vulva and anus may be even higher.[4,6-8]

The appearance of malignancies after RT is obviously related to the duration and dose of immunosuppressive medication.[6,9-11] Immunosuppressants may influence different mechanisms resulting in an increased risk for the development of cancer after RT. Immunosuppressive medication can directly affect DNA by inhibiting repair mechanisms and by causing chromosome strand breaks. This may lead to irreversible DNA alterations and subsequent cancer development.[6,12] Additionally, an immunosuppressive state potentiates oncogenic stimuli such as ultraviolet (UV) light, viruses and chemical carcinogens. UV-radiation can lead to mutations in proto-oncogenes and tumour-suppressor genes. Moreover, it can suppress the local cutaneous immune response by depletion of Langerhans' cells with less antigen presentation and recognition as a result.[13-15] HPV is an important factor in the development of lower genital tract malignancies and might also play a role in the development of cutaneous malignancies (http://www.rivm.nl).[13,15-18] The viral E6 protein inactivates p53 (a tumour-suppressor protein), which results in chromosomal instability and diminished apoptosis. The E7 protein suppresses the retinoblastoma protein pathway, which leads to enhanced cell proliferation.[17,19] In the pathogenesis of skin cancer, E6-proteins can inhibit UV-induced apoptosis by a p53-independent mechanism, which results in accumulation of UV-induced mutations.[13,15-17]

Skin cancer is the most commonly encountered malignancy in RTRs, with 37.4–63% of all post-transplantation tumours.[1,4,6,12,20] In countries with a temperate

climate, the incidence of skin cancer within 10 years after RT is 10–15%. After 20 years, this percentage increases to 40%.[7,21] More than 90% of all skin cancers are non-melanoma skin cancers, which are predominantly squamous cell carcinomas (SCCs) (up to 250-fold increased risk), followed by basal cell carcinomas (BCCs) (up to 10-fold increased risk).[3,7,11,22,23] As BCCs prevail in the general population, the SCC/BCC ratio is reversed in RTRs (http://www.rivm.nl).[7,24]

It is generally accepted that lower genital tract neoplasms in female RTRs are fully related to high-risk HPV (hrHPV). Accordingly, immunosuppressed female RTRs are at a significantly increased risk for abnormal cervical smears, cervical/vulvar intra-epithelial neoplasia (CIN/VIN) and lower genital tract malignancies. As a consequence, prevention and early treatment of (pre)malignancies is important. Earlier publications have suggested conducting physical examinations and cervical smears with smaller intervals than common in the national screening programmes (target population in the Netherlands: 30–60 years of age; interval 5 years), although there is a lack of evidence for this policy.[25-27] In 2000, The American Society of Transplantation advised yearly cervical screening for female RTRs.[26]

In our study, we investigated whether cervical smears were performed in accordance with the advised yearly interval. In addition, we analysed the development of vulvar, vaginal and cervical (pre)malignancies in female RTRs to determine their prevalence in our RTR-population. Moreover, as both cutaneous and female lower genital tract (pre)malignancies are probably associated with HPV infections, we studied the correlation between these (pre)malignancies in the RTR-population. We formulated recommendations to optimise the follow-up concerning lower genital tract (pre)malignancies in female RTRs.

Patients and Methods

Data on all consecutive female patients who underwent a RT between January 1991 and December 1995 at the Radboud University Nijmegen Medical Centre, the Netherlands, were included in this analysis. Identities of all 224 patients were extracted from the local RT registry of this academic centre. Clinical data of the patients were abstracted from the patient hospital charts and the electronic patient files, up to the first of August 2008. To complete the histo- and cytopathological data, we used PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), which is a nationwide histo- and cytopathology network and archive that achieved complete national coverage since 1991.[28] All patients started with triple immunosuppressive therapy (calcineurin inhibitor, mycophenolate mofetil and prednisolone). Six months after transplantation, almost all patients were treated with double immunosuppressive therapy [in most instances azathioprine (2-3 mg/kg) and prednisolone (10 mg)].

The follow-up period was defined as the period between transplantation and any of the following dates whichever is earlier: the first of August 2008, date of death or date denominated as 'lost to follow-up'. Patients with failure of renal graft function (n = 73) and therefore restart of dialysis were also followed until the first of August 2008. Variables recorded included sociodemographic patient characteristics (i.e. race, age at transplantation, decease) and background information on renal medical history, transplantation, and restart of haemodialysis.

We collected the dates and results of cervical smears and the development of skin cancer and cervical, vaginal or vulvar (pre)malignancies after RT. Whenever a malignancy developed, we registered additional clinical and pathological data. The duration of immunosuppression was calculated from the date of transplantation to either the end of the study period, the date of death, or the date of definitive transplant failure when dialysis was resumed. When a patient used immunosuppression during more than one period, the duration of all such periods were aggregated.

We counted the total number of cervical smears performed in female RTRs from their 18th year of life. As the advised screening frequency is once a year, we excluded the patients with less than 1 year of follow-up after their transplantation from further analysis. To calculate the number of patient-years after transplantation, we also corrected the years after the transplantation for incomplete follow-up, death, and childhood (<18 years). The mean number of cervical smears per patient per year was calculated by dividing the total number of cervical smears by the total number of patient-years after transplantation. We compared this ratio with the advised ratio of 1.0 smear per patient-year. The ratio of cervical smears performed before the first low- or high-grade squamous intraepithelial lesion (SIL; after which patients get more frequent follow-up smears according to national guidelines) was calculated by dividing the total number of cervical smears until the first pathological smear by the number of patient-years in that period. Age-adjusted prevalence rates of (pre) malignancies in the studied cohort were calculated per 100.000 individuals using the European Standard Population (as defined by the WHO) for comparative purposes. Data on prevalence of (pre)malignancies in the general population were obtained from national and international literature and from the Netherlands Cancer Registry.

Statistical analysis

Descriptive statistics were used to reproduce study results as percentages, means, medians and standard deviations. To test the correlation between the occurrence of skin cancer and lower genital tract malignancies in female RTRs, a Spearman Rho correlation coefficient was determined. Different ratios of smears per patient-year were compared using Student's *t*-tests. Calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA). *P*-values of <0.05 were considered statistically significant.

Results

The baseline characteristics of the 224 female RTRs are shown in Table 1. The number of transplantations was almost equally divided over the years, and predominantly carried out between the age of 41 and 60 years: the median age of patients at transplantation in our cohort was 44.6 years (range: 5.1 – 74.6 years).

Table 1 Baseline characteristics of renal transplant recipients

	Number of patients	
	N	**%**
Age at transplantation (years)		
0-18	19	8.5
19-40	79	35.3
41-60	104	46.4
> 60	22	9.8
Year of transplantation		
1991	47	21.0
1992	38	17.0
1993	37	16.5
1994	51	22.8
1995	51	22.8
Total renal transplantations		
1	175	78.1
2	43	19.2
> 2	6	2.7

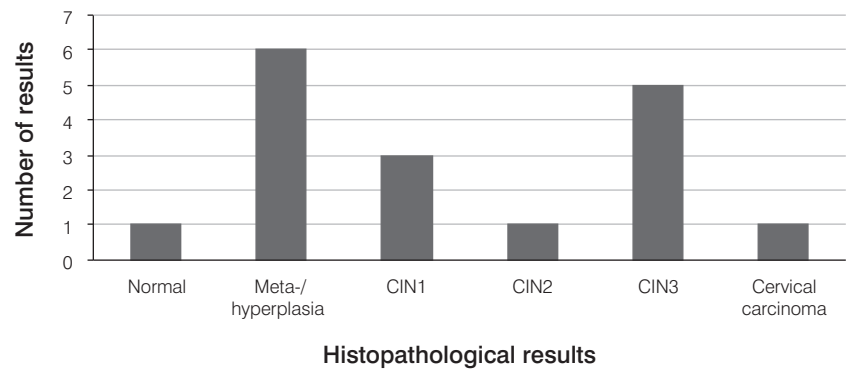
A minority of patients (n = 49, 21.9%) went through more than one RT. Ten patients were lost to follow-up because of transplantation in another transplantation centre (n = 5), emigration (n = 1) or unknown reasons (n = 4). Median duration of follow-up was 12.8 years (range: 0 – 17.6 years) and the median duration of immunosuppression was 11.0 years (range: 0 – 29.6 years). At the end of the follow-up period, 123 patients (55%) were still alive. One hundred and one patients (45%) were deceased, particularly because of fulminant infections and cardiovascular diseases. Median time between transplantation and death was 6.0 years (range: 0 – 14.9 years).

Our cohort consisted of 21 RTRs with less than 1 year follow-up after their 18th year of life. One patient died before the age of 18. Consequently, 202 RTRs remained

available for further analysis. Of these patients, 128 women (63.4%) underwent at least one cervical smear while 74 patients (36.6%) never had a cervical smear after their transplantation. There was only one patient who had a mean screening ratio of 1.0, which implies that the cervical smears were performed at least once a year. Seventy-four patients were screened in accordance with the recommended screening in the general population (once in five years). A mean screening ratio lower than 0.2 was seen in 53 patients, which means that these patients were screened with an interval greater than the recommended population screening interval. Taking all cervical smears (449) and patient-years after transplantation (2198) into account, the overall cervical smear/patient-year ratio after transplantation was 0.2. This ratio is significantly less than the recommended screening ratio of 1.0 for female RTRs ($P < 0.001$), but comparable with the national guidelines for women aged 30–60 years. The mean screening ratio in all RTRs (n = 202) before the detection of any low- or high-grade SIL was 0.13.

We counted 17 histopathological examinations of the cervix performed after an abnormal cervical smear in 11 patients. See Figure 1 for an overview. CIN after renal transplantation was detected in eight patients (3.6%). One patient developed CIN 3 and subsequently CIN 1, a year later. One patient of our cohort developed cervical carcinoma (0.4%). Two patients developed meta- or hyperplasia of the uterine cervix and were excluded from further analysis on cervical pathology. The median interval between first transplantation and the development of CIN was 12.3 years (range: 3.5 – 13.7 years). In the eight RTRs with CIN, the median interval between the first transplantation and the first smear performed was 1.2 years (range: 0.2 – 12.5 years).

Figure 1 Cervical histopathological examinations in 11 patients after renal transplantation



CIN1 = Cervical intraepithelial neoplasia grade 1. CIN2 = Cervical intraepithelial neoplasia grade 2. CIN3 = Cervical intraepithelial neoplasia grade 3

Table 2 Comparison of different prevalence rates between renal transplant recipients and the general population

	Comparison of prevalence rates				
			Transplant recipients	General population	Increased risk
	N	%	Prevalence[a]	Prevalence[a]	Rate ratio[d]
CIN	8	3.6	3454.8	600 - 2000 [b]	1.7 – 5.8
Cervical carcinoma	1	0.4	280.0	88.9 [c]	3.2
Vulvar carcinoma	2	0.9	717.5	14.4 [c]	49.8

CIN, cervical intraepithelial neoplasia
[a]: European Standardized Rate, per 100.000
[b]: Obtained from literature references [25,30,31]
[c]: Obtained from the Netherlands Cancer Registry
[d]: Rate ratio is the age-adjusted rate in renal transplant recipients divided by the rate in the general population

The cervical carcinoma developed 5 years after transplantation at the age of 38 years. The first cervical smear in this patient was performed because of irregular blood loss. Histopathology of a biopsy after colposcopy showed a cervical cancer. The screening ratio before the detection of any low- or high-grade SIL was 0.08 in the RTRs with cervical pathology (n = 9), which did not differ significantly from the ratio in RTRs without cervical pathology (0.13; n = 193) ($P = 0.60$). The mean number of cervical smears per patient-year after RT was 0.53 (SD ± 0.31, range: 0.1 – 1.0), which is significantly higher when compared with RTRs without cervical pathology ($P < 0.001$). No information is available about possible complaints that may have led to cervical cytology.

Eight VIN lesions were detected in four of our RTRs during the study period. All of these lesions were HPV-related VIN types (*usual* VIN). The mean age at presentation of the first VIN lesion was 40.3 years (SD ± 4.6 years). The median interval between first RT and first VIN lesion was 13.3 years (range: 5.1 – 14.4 years). SCC of the vulva developed in two patients of our cohort: 10.2 and 13.8 years after transplantation. No cases of vaginal carcinoma occurred in the female RTRs. There was only one patient

Table 3 Cervical smears and histology of cervix and vulva after transplantation

Years after Tx	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16
Pt																											
1																				L	L-CIN3						
2									N											L-CIN0	N	L-CIN3		N	N		N
3																		L-CIN3	N		N	N	N		N		
4	AU		N				AU		AU-CIN3		N	N	N-VIN3	VIN3		N-VIN3			N			N					
5	AU				N				L	AU-CIN1		L	L	L	L		L			L-CINnVIN3-N			L-VIN3-L		L		
6		N								N											H-CIN3	AU	AU-CIN1VIN2	AU	L		
7	L-CIN0-L	L-CIN1	N																								
8																		AU	AU	L-CIN2							
9				L	H CxCa																						
10					VIN1			N					VIN3		L VCa												
11							N										N					L Vca+VAIN					

N = Normal smear result; AU = Cytologically determined atypical squamous cells of undetermined significance; L = Cytologically determined low-grade squamous intraepithelial lesion of the cervix; H = Cytologically determined high-grade squamous intraepithelial lesion of the cervix; CINn = Histologically determined normal cervix; CIN0 = Histologically determined meta- or hyperplasia of the cervix; CIN1 = Histologically determined cervical intraepithelial neoplasia grade 1; CIN2 = Histologically determined cervical intraepithelial neoplasia grade 2; CIN3 = Histologically determined cervical intraepithelial neoplasia grade 3; VIN1 = Vulvar intraepithelial neoplasia grade 1; VIN2 = Vulvar intraepithelial neoplasia grade 2; VIN3 = Vulvar intraepithelial neoplasia grade 3; VCa = Vulvar carcinoma; CxCa = Cervical carcinoma; | = Deceased; || = End of follow up.

with vaginal intraepithelial neoplasia (VAIN), which occurred simultaneously with SCC of the vulva. Table 2 compares the standardized, age-adjusted prevalence rates of CIN, cervical carcinoma and vulvar carcinoma between transplant recipients and the general population. We were not able to present this comparison for VIN, as no publications concerning prevalence rates of VIN in the general population exist.

Table 3 shows an evaluation of the cervical smears and histology of cervix and vulva after transplantation. The majority of the lower genital tract (pre)malignancies occur after a median interval of 11.5 years (range: 5 – 13.5 years). At least seven RTRs hardly received screening smears before the development of serious cervical/vulvar pathology. In three patients, a relatively short period of time (approximately 2 years) elapsed between the transformation of benign cervical smears to low-grade SIL, leading to CIN in two patients. In the third patient, a vulvar carcinoma and VAIN were diagnosed after the low-grade SIL was detected.

Forty-two out of 224 RTRs (18.8%) developed at least one cutaneous malignancy. Twenty-nine RTRs developed 63 SCCs on non-genital skin. The remaining part of the skin tumours were mostly BCCs. The median interval between transplantation and the first skin malignancy was 6.2 years (range 0.3 – 16.5 years).

There was only one patient with skin cancer who also had vulvar pathology in combination with a VAIN lesion. No significant correlation between skin cancer and lower genital tract (pre)malignancies was found in our RTR population (Spearman Rho = -0.044, SD ± 0.058; $P = 0.508$). The absolute numbers of (pre)malignancies can be found in Table 4.

Table 4 Correlation between lower genital tract (pre)malignancies and skin cancer in renal transplant recipients (absolute count)

Type	Patients (N)	VIN	CIN	VAIN	CxCa	VulvaCa	SkinCa
VIN	4		3	0	0	1	0
CIN	8	3		0	0	0	0
VAIN	1	0	0		0	1	1
CxCa	1	0	0	0		0	0
VulvaCa	2	1	0	1	0		1
SkinCa	42	0	0	1	0	1	

VIN = Vulvar intraepithelial neoplasia; CIN = Cervical intraepithelial neoplasia; VAIN = Vaginal intraepithelial neoplasia; CxCa = Cervical carcinoma; VulvaCa = Vulvar carcinoma; SkinCa = Skin cancer

Table 5 Suggested gynaecological standard screening procedure of cervix and vulva for female renal transplant recipients

	Pre-transplantation	Post-transplantation	
		Normal [1]	Abnormal [2]
Start	0-6 months before RT	Approximately 3 years after RT	Immediate after RT
Frequency	Once	Once a year	Once a year
Screening	Routine*	Routine*	According to current gynaecological guidelines; thereafter routine*

RT = Renal transplantation
[1]: In case of normal pre-transplant screening result.
[2]: In case of abnormal pre-transplant screening result.
* Routine screening comprises anamnesis, inspection and cytology (smear).

Discussion

Our study shows that cervical screening smears in RTRs are not being performed in accordance with the recommended interval of once a year. We confirmed the elevated risk for RTRs to develop vulvar and cervical (pre)malignancies, which developed 5 – 13 years after transplantation. It appears that skin malignancies and gynaecological (pre)malignancies, which are both considered to be related to HPV and more frequent after RT, are not related with each other; of all women who developed skin malignancies (19%), only one vulvar carcinoma combined with vaginal dysplasia was diagnosed.

We investigated the performance of cervical smears in RTRs. The recommended screening interval for RTRs as suggested in previous publications varies between 6 and 12 months (1–2 smears per patient per year)[25-27], although there is no evidence that cervical screening with a short interval (when compared with the national screening programme in the Netherlands: between age of 30 – 60; once in 5 years) will either decrease the incidence of lower genital tract (pre)malignancies or improve the prognosis.

The interval of the smears performed in our cohort was comparable with the national screening programme in the Netherlands, with a mean number of 0.2 smears per patient per year (one smear once in 5 years for each patient). This low number of smears (when compared with the guideline of yearly smears) might be explained by several factors. First, the coverage rate of the national screening programme only

reaches 77%[29], which might be explained by lack of motivation or fear for screening. Therefore, we could not expect a 100% coverage rate in our RTR population. Furthermore, it might be possible that the advice for yearly cervical smears is not well implemented in the daily practice of the nephrologist or the general practitioner, because of lack of evidence for this policy or because of plain inattention. Moreover, patients may avoid cervical screening either because they underestimate the importance of screening or because they find the investigation aggravating.

The ratio of the smears that were performed before the first low- or high-grade SIL was lower (0.13) than the overall screening ratio (0.2). In the years after an abnormal smear, the ratio of smears was higher attributable to the follow-up smears that are required to be performed with more regular intervals according to national guidelines.

We detected CIN lesions in eight patients (3.6%). Previous publications reported the occurrence of cervical dysplasia in 1.28%, 2.0% and 0.6% of the general population in the Netherlands, USA and Canada respectively.[25,30,31] On the basis of these percentages, it seems that our RTRs have at least a twofold to sixfold increased risk of developing CIN, when compared with the general population. This result supports the findings of earlier investigations that showed that the prevalence of CIN is increased in RTRs.[27,32]

Only four patients with dysplasia of the vulva were found. All of the lesions were HPV-related VIN types. Likely, VIN is underreported, because there is no screening instrument for VIN resulting from its low incidence with limited malignant potential. Moreover, RTRs are not routinely asked for vulvar complaints and no standard gynaecological examination is performed. Although pruritus is the most common symptom of VIN, this symptom is frequently misclassified, as RTRs are prone to develop candidiasis, which is the most frequently made diagnosis in case of pruritus. Finally, it might be possible that suspicious lesions are not always histopathologically examined.

Cervical carcinoma was diagnosed in only one patient. Comparing this number with the rates of cervical carcinomas in the age-adjusted standardized general population, the RTRs in the studied cohort have at least a threefold higher risk for developing cervical carcinomas than the general population. A limited number of earlier studies report comparable standardized incidence rates between 3.3 and 8.5.[5,6,33] The cervical carcinoma in our study developed 60 months after transplantation, which agrees with the data reflected in other studies (38–102 months).[5,34]

Carcinomas of the vagina are rare, with a prevalence of 1.7 per 100.000 in the Dutch general population. Based on recently published standardized incidence rates for RTRs for developing vaginal carcinomas (15.8 and 36.0)[5,6], we could have expected 0.06 to 0.14 cases of vaginal carcinoma in our cohort. It is therefore not surprising that we did not diagnose any patients with a vaginal malignancy.

Two patients were diagnosed with SCCs of the vulva, which is an extremely rare disease. This is a 50-fold increased risk compared with the European Standardized Rate of vulvar carcinomas in the general population. Both vulvar carcinomas had usual VIN (related to HPV infection) in the adjacent tissue, which proves a causal relationship between HPV and vulvar carcinoma just like in cervical cancer. Two studies concerning solely vulvar carcinomas demonstrated a 25- to 40-fold increased risk for RTRs to develop vulvar carcinomas.[5,6] An epidemiologic study from Sweden published in 1986 documented a 100-fold increased risk of developing carcinomas of the vulva and anus compared with the general population.[8]

We observed a median interval of 12.3 years (range: 3.5 – 13.7 years) between the first transplantation and the development of CIN. Three earlier studies found an average interval between the beginning of immunosuppressive medication and CIN to be between 38 and 47 months.[25,27,34] The longer interval in our study might be partly explained by demographic differences of the patients in the cohorts studied and use of other immunosuppressive medication. The vulvar SCCs of our cohort developed after an average interval of 144 months (SD ± 30.5 months), which seems to correspond with data reported in the literature.[5,8]

In the nine patients with CIN and cervical carcinoma significantly more cervical smears were performed (0.53 per patient per year; $P < 0.001$) compared with the RTRs without cervical (pre)malignancies. Two explanations for this result can be given. First, a considerable number of low- and high-grade SILs originated in these patients before the CIN lesions were diagnosed; all patients with abnormal cytology or histology will undergo more frequent follow-up smears. Second, patients with cervical dysplasia might have had more gynaecological complaints when compared with the general population. Unfortunately, no information is available on possible gynaecological complaints in this cohort. The screening ratio before the detection of any low- or high-grade SIL in this group of RTRs did not differ significantly from the ratio in RTRs without cervical pathology. Nevertheless, at least five RTRs were screened only barely before the diagnose of serious cervical pathology. Through more frequent follow-up with more smears some of these cervical (pre)malignancies could have been detected earlier.

Immunosuppression has direct carcinogenic effects; it predisposes patients to develop infections and potentiates oncogenic viruses like HPV. Based on the results of earlier publications, it is very likely that HPV infections play a prominent role in the higher incidence of lower genital tract (pre)malignancies in RTRs.[8,25,32,35,36] Halpert *et al.*[25] presented higher rates of HPV infections in transplant patients (8.5 – 17.1%) compared to the general population (1.85%). This finding was confirmed by Brown *et al.*, who reported a significant difference in the presence of HPV-positive lower genital tract neoplasms between female RTRs and an immunocompetent group. For example, 100% of the vulvar lesions in RTRs were HPV-positive compared to 21–57%

in immunocompetent individuals.[35] Furthermore, several studies showed a significantly higher rate of infections with hrHPV subtypes 16 and 18 in lower genital tract malignancies of RTRs when compared with the general population.[32,35] Paternoster *et al.*[36] noted a constant association between those hrHPV types and lower genital tract intraepithelial lesions.

Screening for cervical/vulvar pathology and hrHPV infections just before transplantation is not a common procedure, because the exact timing of transplantation is not planned ahead. As more and more elective kidney transplantations with a kidney from a living donor are performed, it might be possible to introduce a screening just before the date of transplantation for cervical/vulvar pathology and presence of hrHPV infections.

The exact mechanism underlying the high prevalence of HPV infections in RTRs remains unclear. Normally, the majority of HPV infections are transient resulting from clearance from the HPV-infected epithelium. It might be possible that RTRs have a diminished ability to clear new HPV infections because of the impairment of immunological surveillance. This, in combination with high prevalence of HPV subtypes 16 and 18, might additionally lead to more aggressive growth of malignancies. However, it is not likely that RTRs acquire new HPV infections as, based on the average age at transplantation, the majority of the RTRs already had their sexarche long before transplantation. Besides, transplant recipients may be sexually less active than the average population as a result of the burden of their disease. Another, more plausible explanation might be that the beginning of immunosuppressive medication may activate a latent HPV infection, resulting in a rise of the viral load.[37]

The development of cutaneous malignancies, and the interval after which they develop, does not seem to be associated with the development of lower genital tract malignancies and *vice versa*. It might be possible that different HPV types are responsible for the occurrence of malignancies in the genital area and for neoplasms of other skin areas, although the role of HPV in skin cancer remains unclear.[38] Furthermore, other factors (like UV radiation) might play a more important role in the development of non-genital skin malignancies.

Our investigation was conducted as a single-centre study, which implicates a relatively small number of patients. On the other hand, the relatively long follow-up after transplantation is an important strength of our study, as malignancies such as lower genital tract (pre)malignancies hardly occur in the first 5 years after transplantation. A limitation of the retrospective design of our study is the lack of data about lifestyle risk factors (e.g. smoking, riskful sexual behaviour and skin cancer-related risks) and the exact medication schedules (many different schedules with multiple conversions during follow-up). Further prospective investigations and the use of a standardized questionnaire might eliminate this possible bias.

Annual screening for cervical cancer in RTRs using conventional cytology recently proved to be cost-effective.[39] Yearly cervical smears might be combined with a thorough vulvar inspection. Our data suggest that the majority of patients with cervical pathology is diagnosed 9 years after RT. Therefore, it is justified, in our opinion, to postpone the recommended yearly screening to approximately 3 years after RT. This is allowed under the condition that patients are screened on cervical and vulvar pathology and HPV infections before their RT, as pre-RT cervical/vulvar pathology might worsen when immunosuppression is started. This way the 'doctor-density' can be limited in the first years after transplantation when patients and doctors are focussed on preservation of kidney function. If RTRs have abnormal screening results before transplantation, a more intense follow-up schedule should be carried out immediately after RT. Table 5 recapitulates the suggested gynaecological standard screening procedure for female RTRs. It is important to keep in mind that there is no evidence yet that this schedule will decrease the incidence of female genital malignancies.

To conclude, this study emphasises the need for more regular screening for potentially lethal malignancies of the lower genital tract in RTRs, as close and careful monitoring and treatment of suspected lesions may prevent more serious pathology. Additionally, RTRs have to be advised properly about the importance of regular screening and self-examination of the vulvar region.

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CHAPTER

7

Anogenital malignancies in women after renal transplantation over 40 years in a single centre

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Abstract

Background

Renal transplant recipients have an increased risk to develop human papillomavirus (HPV)-related anogenital malignancies. A clinical overview of female anogenital posttransplantation malignancies and possible multifocal premalignancies over a period of 40 years renal transplantation is presented. Additionally, the genotype-specific prevalence of HPV in these (pre)malignancies was investigated.

Methods

Data of 1023 women, who underwent a renal transplantation between 1968 and 2008, were collected. Clinical data of all female renal transplant recipients who developed anogenital malignancies were retrospectively analysed. The histology, cytology, and distribution of genotype-specific HPV infections were analysed in all primary anogenital tumours and possible (multifocal) premalignancies.

Results

Sixteen anogenital malignancies (1.6%) were found: vulva ($n = 6$), cervix ($n = 5$), and anus ($n = 5$). Twelve of 16 patients never had a cervical smear before transplantation. The median interval between transplantation and diagnosis of malignancy was 136 months (range: 16 – 288 months). High-risk HPV was detected in 91.7% of investigated lesions, HPV subtype 16 predominated (54.5%). Four of seven patients with two distinct anogenital lesions had different HPV types in the lesions.

Conclusions

A high number of anogenital malignancies developed in our cohort, which are nearly all caused by HPV. Multifocal lesions within one patient frequently contained different high-risk HPV genotypes in both lesions. Our results underline the importance of anogenital screening and monitoring before and periodically after renal transplantation to prevent morbidity and mortality from anogenital malignancies.

Introduction

Renal transplantations (RTs) account for the major part of solid organ transplantations that are performed worldwide. In 2010, more than 850 RTs were performed in the Netherlands (16 million inhabitants) according to the Netherlands Organ Transplantation Registration.[1]

In general, solid organ transplantation requires the use of lifelong immunosuppressive medication. Because of the improvement of immunosuppressive regimens, the current 1-year patient and graft survival is more than 90% and the incidence of acute rejection has decreased to 10-15%.[2,3] As a result of the enhanced long-term transplant survival and the increasing age of renal transplant recipients (RTRs), the development of cancer is becoming a major cause of morbidity and mortality after RT. A clear association between the duration and dose of immunosuppressive medication and post-transplant malignancies is known.[4-7]

RTRs have at least a threefold to fivefold increased risk to develop any type of cancer compared with the general population.[7-10] The relative risk for specific cancers, such as skin cancer, Kaposi's sarcoma, and post-transplant lymphoproliferative disorders may even be higher.[7-9,11-13] Moreover, many authors have established a significantly increased risk for human papillomavirus (HPV)-associated dysplasia and cancers of the anogenital tract (cervix, vagina, vulva, and anus) in female RTRs.[7-9,14-24] Recently, we found a remarkably increased risk for cervical intraepithelial neoplasia (CIN) (twofold to sixfold), cervical carcinoma (threefold), and vulvar carcinoma (50-fold) in a population of 224 female RTRs who underwent a RT between 1991 and 1995 in our centre.[18] As a consequence of this increased risk, several publications and international guidelines[17,18,25-28] have implemented the advice to intensify cervical screening in those patients by means of smaller intervals than common in many national screening programmes (target population in the Netherlands since 1996: 30 – 60 years of age; interval 5 years).

It was previously documented that RTRs are more often affected with (multifocal; i.e. having two or more localisations of the anogenital tract, synchronously or metachronously within a single patient) HPV infections compared with the general population.[14,15,17,27,29,30] Persistent infections with high-risk HPV (hrHPV) types (the majority HPV 16 and 18) are important risk factors for cervical cancer development.[31] Additionally, HPV is etiologically related to a number of cancers of the anus and vulva.[31-37] Of all anal carcinomas, 71% to 88% are positive for HPV, with a preponderance of hrHPV types.[38-40] Vulvar squamous cell carcinoma (SCC) and its precursor lesions may originate from an HPV-independent or an HPV-dependent pathway. Carcinogenesis of the HPV-dependent (generally HPV type 16 and 18) pathway largely resembles that of cervical SCCs. This type of vulvar cancer primarily affects younger women and encompasses the minority of vulvar SCCs in the general

population (only ~20%). Conversely, HPV-dependent vulvar SCCs seem to comprise the majority of vulvar carcinomas in immunocompromised women.[33,41]

A long-standing hrHPV infection may cause multifocal (pre)malignancies of the anogenital tract.[31] It was recently shown that in the general population frequently identical HPV types are found in both vulvar and cervical (pre)malignancies within the same patient, even after an interval of more than 10 years.[42] Hence, a patient with a hrHPV-related anogenital (pre)malignancy is at higher risk to develop other hrHPV-related anogenital (pre)malignancies.

The elevated risk for RTRs to develop HPV-related anogenital (pre)malignancies may result in severe morbidity and mortality, mainly as these lesions may give rise to major dilemmas regarding therapy as radiation therapy or extensive surgery may harm the renal transplant. Therefore, understanding the elevated risk, the role of HPV, prevention and early treatment of premalignant lesions in this vulnerable patient population is important.

In this report we aim to give a clinical overview (including treatment) of all incident cases of anogenital malignancies after RT in our centre which has 40 years of experience with RT. Additionally, the HPV genotype distribution in all these malignancies and possible (multifocal) premalignancies within the same patient will be determined. Finally, we offer practical advice to improve the future health and quality of life of female RTRs.

Materials and Methods

Data sources

Data of all consecutive female RTRs who underwent a RT in the Radboud University Nijmegen Medical Centre, the Netherlands, between January 1968 and December 2008 were collected. We assembled sociodemographic patient characteristics, medical data on RT, and on incident cases of malignancies of the female lower anogenital tract (i.e. cervix, vagina, vulva and anal canal), up to the end of July 2010. Total duration of transplant function of all patients of our cohort was analysed, taking into account repeated RTs in one patient. Patients with a total duration of transplant function less than 90 days were excluded from further analyses.

Histo- and cytological data were obtained from the Pathological Anatomical National Automated Archive, which is a nationwide histo- and cytopathology network and archive that covers the entire country since 1991.[43] Medical charts and electronic patient files were used to complete medical data.

Patients with malignancy of the lower anogenital tract: clinical characteristics

Data of female RTRs with a malignancy of the lower anogenital tract were registered: localisation and histopathological type of malignancy, date of diagnosis, history of (pre)malignancies and cervical smears, treatment, recurrence or metastases of the tumour after treatment. In case of development of anogenital premalignancies pre- or post-malignancy, the histopathological type, localisation, and date of diagnosis were registered. If applicable, we also collected the date and cause of death. Patients were followed until the date denominated as 'lost to follow-up', date of decease, or the end of July 2010.

HPV presence and genotyping

Specimens of all primary anogenital tumours were available for detection of genotype-specific HPV infections. Whenever there was an interval of at least 6 months between diagnose of the tumour and of previous or subsequent (multifocal) premalignant lesions, we also determined the distribution of HPV genotypes in these lesions. We choose an interval of 6 months to make probable that both lesions were separate entities.

DNA was isolated from formalin-fixed, paraffin-embedded tissue sections (6 μm) with the EZ1 robot (with the DNA tissue kit of Qiagen) according to standard procedures[44] and used for polymerase chain reaction (PCR) analysis. A negative water control was included with each batch of 10 samples. Broad-spectrum HPV DNA amplification was performed using a short PCR fragment (SPF-PCR) assay. The SPF-PCR system amplifies a 65-bp fragment of the L1 open reading frame, allowing the detection of at least 43 HPV types. In case of a positive PCR result, subsequent HPV genotyping was performed using a reverse hybridisation line probe assay (LiPA), allowing simultaneous typing of 25 HPV genotypes. The combined SPF-PCR-LiPA system for detection and genotyping of HPV has been described in detail elsewhere.[44] As a quality control for the presence of DNA and absence of PCR inhibitors in the isolated material, a –globin PCR was performed as described earlier.[45]

Statistical analysis

Descriptive statistics were used to reproduce study results as percentages, means, medians, standard deviations, and ranges. Calculations were performed using Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA).

Results

Baseline

During the study period, 1253 RTs were performed on female patients at the Radboud University Nijmegen Medical Centre. One hundred twenty-seven patients were transplanted more than once, with a maximum of four RTs per patient. For this analysis, patients were considered only once, whether they received multiple RTs or not. A total duration of renal transplant function less than 90 days was seen in 81 patients, who were excluded from further analysis. Consequently, the final cohort included a total of 1023 consecutive female patients whose data were suitable for analysis. Baseline characteristics are reflected in Table 1. Transplantations were predominantly carried out between the age of 40 and 60 years. The median age at first RT was 44.5 years (range: 3.5 – 74.6 years).

Malignancies of the Female Lower Anogenital Tract

Sixteen patients in our cohort (1.6 %) developed an anogenital malignancy (see Table 2 for a detailed overview of all patients). All but one of these patients were transplanted once; patient 6 went through two RTs. The majority of the patients started with double immunosuppressive therapy (prednisolone and azathioprine or cyclosporine). Seven patients who experienced acute rejections were all successfully treated with prednisolone or antithymocyte globulin.

Six vulvar, five cervical, and five anal de novo carcinomas were diagnosed. The majority of the malignancies were SCCs. One adenocarcinoma of the anus was observed (patient 12). One patient (patient 12) developed a high-grade liposarcoma with unknown localisation 18 years before transplantation. This tumour was excised without any recurrence or metastases. Five patients (patient 1, 2, 4, 10, and 15) developed multiple post-transplant (pre)malignant skin lesions on non-genital skin before and after the diagnosis of their anogenital malignancy. Patient 1 and 14 developed a Merkel cell carcinoma of the skin and an adenocarcinoma of the colon, respectively, 3 months and 5 years before the diagnosis of their vulvar carcinomas. The colon carcinoma showed local recurrence without metastases 2 years after initial treatment and was treated with local resection. Patient 15 had been successfully treated for breast cancer 13 years before the diagnosis of her anal carcinoma.

The median age at diagnosis of the anogenital malignancies in our cohort was 45 years (range: 37.2 – 72.5 years). The median interval between RT and diagnosis of malignancy was 136 months (range: 16 – 288 months). At the end of our study, seven patients were free of disease, five patients died of the disease, and four patients died of another cause. The median age at death was 53.2 years (range: 40.4 – 79.9 years). Table 3 presents data separated for the various types of the anogenital malignancies in our cohort.

Table 1 Baseline characteristics of female renal transplant recipients between 1968 and 2008 (n = 1023)

	All patients (*n* = 1023)		Cases (*n* = 16)		Others (*n* = 1007)		
	N	(%)	N	(%)	N	(%)	*P*
Age at first transplantation (yr)							
0 – 18	102	10.0	-	-	102	10.1	
18 – 40	325	31.8	10	(62.5)	315	31.3	
40 – 60	473	46.2	4	(25.0)	469	46.6	
≥ 60	123	12.0	2	(12.5)	121	12.0	
Mean (SD)	41.7	(16.2)	39.1	(16.0)	41.7	(16.2)	0.621 [a]
Year of first transplantation							
1968 – 1978	78	(7.6)	2	(12.5)	76	(7.5)	
1978 – 1988	220	(21.5)	5	(31.3)	215	(21.4)	
1988 – 1998	385	(37.6)	6	(37.5)	379	(37.6)	
1998 – 2009	340	(33.2)	3	(18.8)	337	(33.5)	
Total number of RTs							
1	898	(87.8)	15	(93.8)	883	(87.7)	
2	106	(10.4)	1	(6.3)	107	(10.6)	
>2	19	(1.9)	-	-	19	(1.9)	
Cause of end-stage renal disease							
Chronic glomerulonephritis	181	(17.7)	4	(25.0)	177	(17.6)	
Polycystic kidney disease	143	(14.0)	2	(12.5)	141	(14.0)	
Chronic pyelonephritis	142	(13.9)	1	(6.3)	141	(14.0)	
Diabetic nephropathy	48	(4.7)	3	(18.8)	45	(4.5)	
Others	429	(41.9)	6	(37.5)	423	(42.0)	
Unknown	80	(7.8)	-	-	80	(7.9)	
Total time on dialysis (days) [b]	816	(1 – 6976)	444	(30 – 3091)	832	(1 – 6976)	0.046 [c]
Duration of transplant function (yr) [d]	10.1	(7.8)	15.2	(9.2)	10.0	(7.7)	0.008 [a]
Acute rejection [e]	513	(50.1)	11	(68.8)	502	(49.9)	0.134 [f]
ATG induction therapy	102	(10)	4	(25.0)	98	(9.7)	0.066 [f]

[a] Independent Student's *t*-test. [b] Data are given in median (range). [c] Mann-Whitney *U* test. [d] Data are given in mean (±SD). [e] Number of patients with at least one acute rejection treated with methylprednisolone. [f] Pearsons' Chi-square test. RTs = Renal transplantations; ATG = Antithymocyte globulin

Table 2 Detailed information on female renal transplant recipients with anogenital malignancies

Patient	Age at first RT (yr)	Localisation	Tumour Type	Age at diagnosis (yr)	Other malignancies	Therapy	Recurrence	Follow up since diagnosis
1	19.1	Vulva	SCC	43.1	Skin and MCC	Radical vulvectomy and lymphadenectomy	-	FU 19 M COD: metastatic MCC
2	23.5	Vulva	SCC	41.4	Skin	Partial vulvectomy and lymphadenectomy	Vulva	FU 141 M DOD
3	24.9	Vulva	SCC	44.7	-	Radical vulvectomy and lymphadenectomy	-	FU 138 M NED
4	34.0	Anus	SCC	44.3	Skin	RT	Anus	FU 37 M DOD
5	56.9	Anus	SCC	69.3	-	External + internal RT and Chemo	-	FU 127 M COD: Unknown
6	29.4	Anus	SCC	45.3	-	Excision	-	FU 138 M NED
7	65.4	Cervix	SCC	69.7	-	Wertheim-Okabayashi + RT	Vagina	FU 32 M DOD
8	29.1	Vulva	SCC	39.3	-	Radical vulvectomy and lymphadenectomy + partial sigmoid resection +rectumamputation	-	FU 13 M COD: Acute myelofibrosis
9	33.6	Cervix	SCC	38.6	-	Wertheim-Meigs with ovariectomy	-	FU 132 M COD: Myocardial infarction
10	28.9	Vulva	SCC	42.8	Skin	Partial vulvectomy	-	FU: 24 M NED
11	49.5	Cervix	SCC	59.3	-	Wertheim-Meigs with ovariectomy	-	FU: 2 M DOD
12	71.2	Anus [a]	AC	72.5	Liposarcoma	RT, chemo and rectum amputation	-	FU: 13 M DOD
13	58.1	Cervix	SCC	60.2	-	Wertheim-Meigs + RT	-	FU: 47 M NED
14	46.6	Vulva	SCC	68.1	Colon	Partial vulvectomy and lymphadenectomy	-	FU: 4 M NED
15	34.8	Anus	SCC	52.7	Skin & Mamma	Rectum amputation	-	FU: 13 M NED
16	29.6	Cervix	SCC	37.2	-	Wertheim-Meigs	-	FU: 7 M NED

[a] Liver metastasis was already present at time of diagnosis AnusCa. RT = Renal transplantation; FU = Follow-up; M = Months; COD = Cause of death; NED = No evidence of disease; SCC = Squamous cell carcinoma; MCC = Merkel cell carcinoma; DOD = Dead of disease; AC = Adenocarcinoma; VCa = Vulvar carcinoma; CxCa = Cervical carcinoma; AnusCa = Anus carcinoma; RT = Radiotherapy; Chemo = Chemotherapy

Table 3 Characteristics of post-transplant anogenital malignancies

Location	Median age at diagnosis, years (range)	Median interval RT- malignancy, years (range)
Anus	52.7 (44.3-72.5)	12.4 (1.3-17.8)
Vulva	42.9 (39.3-68.1)	18.8 (10.2-24.0)
Cervix	59.3 (37.2-69.7)	5.0 (2.2-9.8)

RT = Renal transplantation

Four of five patients with cervical cancer (patient 7, 11, 13, and 16) had modified surgical procedures, with only unilaterally removed pelvic lymph nodes and parametric tissue because of the presence of the renal transplant on the other side of the pelvis. Radiotherapy was indicated but abandoned to preserve renal function in patient 16. Patient 13 lost renal transplant function as a result of radiotherapy and is currently on dialysis.

Evaluation of last cervical smear before and first cervical smear after RT in the 16 patients is presented in Table 4. It shows that 12 of 16 patients never had a cervical smear before their transplantation. Among the four patients who underwent at least one cervical smear before transplantation (interval between last smear and RT ranging between 1 and 7 years), there was one patient with a cytological normal cervix 3 years before RT that was diagnosed with a cervical carcinoma approximately 2 years after RT. Patient 11 was diagnosed with a CIN 3 lesion before RT. After RT, a cytological high-grade squamous intraepithelial lesion of the cervix was diagnosed again. However, an intentional wait-and-see policy was carried out, and she was diagnosed with a cervical carcinoma 118 months after her RT.

Nine patients only had cervical smears after RT; in three of them, the first cervical smear was even more than 10 years after transplantation. Five patients were diagnosed with a high-grade cervical lesion (CIN 3) at the moment of first cytological cervical screening after RT (interval between RT and first smear ranging between 3 and 17 years).

HPV Prevalence and Genotype

An overview of the distribution of HPV genotypes in (multifocal) anogenital (pre) malignancies of female RTRs related to time periods before and after renal transplantation is given in Table 5. Of the 16 patients with anogenital malignancies, seven patients developed a premalignant lesion in the anogenital region as well. Of these seven patients, six developed CIN before their malignancy and one (patient 2) developed

Table 4 Cervical smears and histology of cervix before and after renal transplantation

Patient	Cervical smear	Interval before RT (M)	Subsequent histopathological diagnosis	RT	Cervical smear	Interval after RT (M)	Subsequent histopathological diagnosis
1	—				H	202	CIN 3
2	—				L	168	
3	—				H	125	CIN 3
4	—				H	37	CIN 3
5	—						
6	—				H	89	CIN 3
7	—						
8	—				L	78	
9	—				H	59	CIN 3
10	L	17			L	73	
11	H	61	CIN 3		H	41	[a]
12	L	84					
13	L	31			H	26	CervixCa
14	—				L	28	
15	—						
16	—				L	8	

[a] Wait and see policy, no histology of cervix available.
L = cytological determined low-grade squamous intraepithelial lesion of the cervix
H = cytological determined high-grade squamous intraepithelial lesion of the cervix
M = Months

Table 5 HPV prevalence and genotype in (multifocal) anogenital (pre)malignancies of female RTRs related to time periods before and after renal transplantation

Patient	Histo-pathology	HPV	Type	Interval before RT (M)	RT	1st Interval after RT (M)	Histo-pathology	HPV	Type	Interval after 1st interval (M)	Histo-pathology	HPV	Type
1					|	203	CIN3	+	58	85	VulvaCa	+	58
2					|	215	VulvaCa	+	**16**	80	CIN1	+	**59**
3					|	128	CIN3	[a]		109	VulvaCa	+	33
4					|	45	CIN3	+	**6,16**	78	AnusCa	+	**58**
5					|	149	AnusCa	+	16				
6					|	89	CIN3	+	**52**	101	AnusCa	+	**16**
7					|	52	CervixCa	+	56				
8					|	122	VulvaCa	+	16				
9					|	61	CervixCa	+	16				
10	CIN 2	+	16	34	|	166	VulvaCa	+	16	0	CIN1	+	16
11	CIN 3	+	**51**	59	|	118	CervixCa	+	**16**				
12					|	16	AnusCa	-					
13					|	26	CervixCa	+	18				
14					|	258	VulvaCa	+	X				
15					|	214	AnusCa	+	16				
16					|	91	CervixCa	+	16				

[a] β-globin negative, unknown HPV status

M = Months; CIN = Cervical intraepithelial neoplasia; RT = Renal transplantation; VulvaCa = Vulvar carcinoma; CervixCa = Cervical carcinoma; AnusCa = Anus carcinoma; HPV = Human papillomavirus; X = Unknown type

CIN afterward. Patient 10 was diagnosed with an additional CIN 1 lesion at the time of diagnosis of her vulvar carcinoma as well.

Of the 24 investigated (pre)malignant lesions, HPV was detected in 22 (91.7%). HPV type 16 predominated, with 12 of 22 lesions being positive for this type of HPV (54.5%). Nine lesions contained other hrHPV types. One vulvar carcinoma (patient 14) showed HPV positive for an unknown HPV genotype. Four of the seven patients with multifocal anogenital lesions had different HPV genotypes in the different lesions (57.1%). Two of the seven patients had the same HPV types in both lesions and in one patient (patient 3), one of the lesions showed repeatedly –globin negative after DNA extraction. Therefore, the HPV status could not be determined.

Discussion

This long term follow-up study on a large cohort of female RTRs gives an overview of the development of anogenital malignancies after transplantation. We found five cervical, six vulvar, and five anal carcinomas. Especially vulvar carcinomas developed more often and at a younger age compared with the general population. Analysis showed presence of HPV in nearly all lesions, all concerning high-risk genotypes. Multifocal lesions within one patient frequently contained different hrHPV genotypes in both lesions.

The cases in our study had a significantly longer duration of transplant function compared with the other RTRs, and probably longer immunosuppressive use as a consequence. Also, the high number of other (second or third) carcinomas in our cohort is remarkable, which is probably also a consequence of long-term immunosuppression use. The incidence of 1.6% that was found in our cohort seems higher than the overall occurrence of anogenital malignancies in the general population. A rough calculation, not adjusted for age or follow-up years, with the numbers recorded by the Netherlands Cancer Registry shows an estimated raised risk of fivefold for cervical, 41-fold for vulvar, and 122-fold for anal carcinoma in our cohort. If age-adjusted calculations had been performed, the risks would probably even be higher, because of the relatively young age at diagnosis of anogenital malignancies in our cohort. Moreover, as the Pathological Anatomical National Automated Archive has only complete national coverage since 1991, it is possible that the total number of anogenital (pre)malignancies in our cohort is even underreported.

The median age at diagnosis of vulvar SCC in the Dutch general population is 70.4 years.[46] In the current study, five of six RTRs developed a vulvar carcinoma at approximately 40 years of age, which is remarkably young. However, this young age is in agreement with the finding that all these vulvar carcinomas originated from the HPV-dependent pathway. Comparably, an earlier publication reported a 100% HPV

infection rate among RTRs with vulvar carcinomas, compared with a 20% to 57% HPV infection rate in vulvar neoplasms of immunocompetent patients.[27,47] Generally, HPV types 16 and 33 are considered to be the most common genotypes in vulvar lesions (present in ~60% and 20% of vulvar carcinomas in the general population, respectively), although other hrHPV subtypes such as 18, 52, and 58 also have been reported.[33,42,47] This corresponds to the types that predominantly have been detected in our cohort (HPV type 16 [50%], 33 [17%], and 58 [17%]).

Surprisingly, there is a difference in the interval times between transplantation and malignancy between the different anogenital cancer types in our cohort. It seems that, in the general population, the rate of malignant transformation of HPV-related vulvar and anal premalignancies is much lower compared with cervical premalignancies.[41,48,49] However, as there are no screening programmes and frequently no histopathological examination is performed for vulvar and anal intraepithelial lesions, the mean interval times between HPV infection and the development of these malignancies remain largely unknown. The median interval between RT and the diagnosis of cervical carcinoma in our cohort appeared to be very short. As anogenital malignancies do not develop over such a short period in general, it is attractive to speculate that those RTRs already had asymptomatic dysplastic cervical lesions at the time of their RT, followed by rapid progression towards invasive carcinoma after the beginning of immunosuppressive therapy. Evaluation of cytological cervical screening in the cases with anogenital malignancies showed that only occasionally cervical smears were performed before RT. Screening of all women before RT would enable to diagnose possible anogenital (pre)malignancies at an early stage and provide adequate treatment for these lesions. However, it may also be possible that HPV-related cervical cancer develops faster in immunosuppressed patients compared with the general population. Because the majority of the cases were diagnosed with invasive lesions, it is difficult to draw a conclusion with respect to transformation rate in these cases.

Various publications and international guidelines advise at least yearly cervical screening with pelvic examination and cervical smear after RT.[17,18,25-28] Wong et al.[50] have shown that this policy is effective in reducing cancer-specific mortality in RTRs. However, yearly follow-up smears were by no means regular in our cohort. This is in concordance with the low cervical screening rate in a previously studied larger cohort of female RTRs.[18] In that study, no differences in screening rate before the detection of any low- or high-grade cervical lesion were seen between RTRs with cervical pathology and those without.[18] The disappointing screening intensity may possibly be explained by the fact that these relatively recent guidelines were not well implemented in the former cohort. However, even though our overview of cervical screening is limited to a subgroup of RTRs with proven anogenital disease, we believe that the high number of high-grade cervical lesions at the time of the first cervical

smear after RT point at the importance of regular cervical screening in RTRs. Especially because the treatment of these malignancies in RTRs frequently requires concessions such as modified surgery or omission of radiotherapy, which may result in a negative outcome.

The observation of HPV infection in women at older ages may be explained by true new infections or by reactivation of a latent infection.[51] It is known that reduced immune surveillance secondary to HIV progression may trigger viral reactivation and may ultimately lead to progression of dysplasia.[52] Presumably, the beginning of immunosuppressive medication in RTRs probably has the same effect, resulting in a rise of the viral load and progression to (pre)malignancies.

Almost 92% of our investigated samples showed a hrHPV infection. hrHPV type 16 was detected in particular (12 of 22; 54.5%), which corresponds with the preponderance of HPV subtype 16 in cervical, vulvar, and anal cancer in the immunocompetent population (50% – 70%).[33,42,47,53] However, less common hrHPV types (e.g. 52, 56, and 58) were present as well. Brown et al.[27] found an obviously higher HPV prevalence in specimens of RTRs (65%) compared with specimens of immunocompetent patients (38%). The high number of hrHPV-positive cases in our study emphasises this finding. Because only specimens of histopathologically proven (pre) malignant lesions were analysed in our study, a large number of female RTRs probably have undetected HPV infections or even (pre)malignant anogenital lesions; in particular, when considering that vulvar- and anal intraepithelial neoplasia (AIN) were frequently not histopathologically examined in earlier daily practice. This emphasises the importance of regular cervical surveillance combined with close inspection of the anogenital area for female RTRs, as we recently advised[18,54]; especially as 11 of the 16 diagnosed malignancies in our cohort developed in the external anogenital area that should be suitable for close observation.

Anal SCC is biologically very similar to cervical cancer. Its precursor lesion (high-grade AIN) is analogue to high-grade CIN. Besides, both anal cancer and AIN are strongly associated with HPV infection. Several studies reported a detection rate of HPV in invasive anal cancers between 71% and 88%.[38-40] Oncogenic HPV subtype 16 predominates, detected in approximately 70% of the HPV-positive anal tumours.[38-40] RTRs are obviously at higher risk of developing anal HPV infection and neoplasia compared with the general population.[55] It is interesting to note that, in this study, hrHPV subtypes (16 [66.7%] and 58 [33.3%]) were present in all three anal SCCs. The only HPV-negative anal carcinoma found was of the adenocarcinoma type. This corresponds with other studies that suggest that a large part of anal adenocarcinomas are not HPV-related.[38-40]

Seven RTRs developed a second anogenital lesion at least 6 months before or after the diagnosis of their anogenital malignancies. Of these patients, only two showed identical hrHPV types in both lesions. In contrast, four patients (57.1%) had

different hrHPV genotypes in both lesions. Compared with earlier research in our centre on nearly only immunocompetent patients with HPV-related vulvar cancer and additional cervical abnormalities (89% of patients with identical, and no patients with different HPV types in both lesions)[42], our immunocompromised cohort showed a remarkably high number of patients with different hrHPV genotypes in both lesions. As time intervals and severity of the lesions did not differ significantly between both cohorts, it is highly possible that the difference in immune status causes the dissimilarities found.

Hampl et al.[56] recently published a hypothesis regarding different pathogenetic mechanisms leading to the development of multifocal anogenital lesions. They stated that immunocompromised patients are characterised by multiple genital lesions caused by different HPV types, including types that are untypical for high-grade lesions. So, an immunocompromised host would be target for repeated independent infections with various HPV types that induce independent lesions.[56] Our findings support this hypothesis.

As we stated earlier, the major role of HPV in the oncogenesis of anogenital (pre) malignancies and the increased risk for these lesions in RTRs strengthen the importance of studying the role of hrHPV vaccination for women before transplantation.[54] The available vaccines (containing hrHPV types 16 and 18) seem to have great potential in the prevention of hrHPV-related anogenital (pre)malignancies in transplant recipients. The present study shows that the relative contribution (= the percentage of positive samples for a specific HPV type in relation to all the HPV-positive samples) of hrHPV genotypes 16 and 18 in anogenital lesions of female RTRs (13 of 22; 60%) approaches the relative contribution of these genotypes in invasive cervical cancer in the general population (71%).[57] Nevertheless, it is conceivable that patients with end-stage renal disease and transplant recipients may be less responsive to the vaccine than immunocompetent individuals, as they may not produce the required protective immune response.[50,58] At present, no data about effectiveness or safety of the HPV vaccination in RTRs are available and prospective studies to elucidate possible clinical benefits of this vaccination in RTRs are needed.

A high number of RTRs was included in our study. Although the follow-up period was extensive for most patients, we must acknowledge that recently transplanted patients had a relatively short period of follow-up. It is known that anogenital malignancies do not develop over such a short period in general. Therefore, the numbers of anogenital malignancies in our cohort can be underestimated and may rise in the future. Nonetheless, we believe that our large and representative population of female RTRs, despite the lack of a control group, gives important insights in the problem of post-transplantation anogenital malignancies.

To conclude, anogenital malignancies are relatively frequently seen in female RTRs, with a crucial role for infections with various (uncommon) hrHPV subtypes.

Frequent complete gynaecological examination, including inspection of the anogenital area, may contribute to early detection of these (pre)malignancies of the anogenital tract of women. These relatively simple tools should therefore be implemented both before and periodically after RT to improve general health and quality of life of female RTRs. Besides, our findings give rise to further research into the course of HPV infections in a larger cohort of RTRs, preferentially in a prospective setting.

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CHAPTER

8

Cervicovaginal HPV-infection in female renal transplant recipients: An observational, self-sampling based, cohort study

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Abstract

Immunosuppressive treatment of organ transplant recipients is associated with an increase in the occurrence of human papillomavirus (HPV) related anogenital (pre) malignancies. This cohort study investigated the genotype-specific prevalence of HPV infections in a large cohort of female renal transplant recipients (RTRs). Participants self-collected a cervicovaginal sample for detection and genotyping of HPV. Besides, they completed a questionnaire regarding sociodemographic variables, medical data and sexual behaviour. Anogenital screening was offered to all HPV positive participants. A total number of 218 female RTRs was included. The prevalence of mucosal HPV infections was 27.1% and 17.4% for high risk HPV in particular. The studied cohort showed a broad range of HPV genotypes and multiple HPV genotypes were found in 27.1% of HPV-positive patients. Seven participants were identified with occult premalignant anogenital lesions. In conclusion, this study shows a high point-prevalence of HPV in female RTRs (age-matched West-European general population: 9-10%) with a shift in the distribution of genotypes as compared with the general population. Moreover, a substantial number of patients with occult pre-malignancies was identified. The introduction of self-sampling for HPV positivity can help in early detection of (pre)malignant anogenital lesions in this vulnerable population.

Introduction

Current immunosuppressive regimens have improved long-term graft and patient survival after renal transplantation. The down-side of prolonged immunosuppressive treatment is an increase in the cumulative occurrence of (pre)malignancies, especially those associated with viral infections.[1,2]

Previous studies reported an increased risk for human papillomavirus (HPV) related anogenital (pre)malignancies in renal transplant recipients (RTRs). A three to six-fold increased risk was found for cervical cancer, a ten-fold increased risk for anal cancer, and even a 31 to 100-fold increased risk for cancer of the vulva.[1,3-5]

Although data on the prevalence of HPV infections in RTRs are scarce, an evident increase compared to healthy immunocompetent individuals has not been found in previous studies.[6-8] Therefore, it is assumed that the elevated risk for developing HPV-related lesions after renal transplantation mainly results from the declined cell-mediated immunity caused by the use of immunosuppressive therapy. However, detailed data on the genotype-specific prevalence of HPV, risk factors for HPV infection, and the relationship between HPV genotypes and anogenital lesions in RTRs are not available.

Recently, a self-sampling technique for HPV detection has been introduced. A number of studies showed that there is a high level of concordance between the results obtained with self-collected samples and physician collected samples.[9-12] Advantages of self-sampling are that it is easy to use, inexpensive, and highly accepted by women.[9-12]

In the present study we employed self-sampling to investigate the genotype-specific prevalence of HPV infections and to offer HPV-based screening for anogenital lesions in a large cohort of female RTRs.

Methods

Study population

Female RTRs that fulfilled the following criteria were invited to participate in this study: (1) transplantation at the Radboud university medical center (RUMC), Nijmegen, or the Maastricht University Medical Centre (MUMC), Maastricht, the Netherlands, in the period 1968-2008, (2) a functioning donor kidney on February 2012, (3) living in the Netherlands, and (4) aged above 18 years. This study was approved by the local medical ethics committees of both participating centres [protocol number: 2011/268] and was conducted according to the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH).

A total of 407 (RUMC) and 219 (MUMC) patients were eligible for participation and were sent written information regarding the study. Of the 626 invited participants,

253 RTRs (40%) (172 RUMC and 81 MUMC) gave their written informed consent for this study. To ensure pseudonymous data handling, all participants were given a unique study code.

Clinical data of the participants regarding the underlying renal disease, dialysis, renal transplantation, immunosuppressive medication, acute rejection episodes and creatinine level at the time of participation were abstracted from the local renal transplantation registries of the two centres.

Sampling technique

All participants were asked to self-collect a cervicovaginal sample in the privacy of their own home with the dry Evalyn Brush® system (Rovers Medical Devices B.V., Oss, the Netherlands), which was proven to provide similar results as a physician-taken sample for high risk HPV (hrHPV) detection.[9] Patients received the collection device, written instructions with illustrations and a return package comprising a leak proof seal bag, absorption sheet and a plastic return envelope complying with the packing instruction for the sending of biological substances (category B) per mail. All samples were stored dry and certified with the unique study code. Specimens were collected from April – November 2012 (RUMC) and January – March 2013 (MUMC).

Specimen preparation and DNA extraction

The dry Evalyn Brush was resuspended in 1·5 ml Thin Prep. The vials were vortexed for 3x15s, stored overnight at 4°C, and again vortexed for 2x15s. From each resuspended dry specimen, 200 μl was used for DNA extraction with the MagNaPure 96 (Roche Molecular Diagnostics). The purified DNA was eluated in 50μl TE-buffer.

HPV detection and genotyping

For detection and genotyping of HPV, broad spectrum HPV amplification was performed using a highly sensitive short-PCR-fragment assay (SPF_{10} -$LiPA_{25}$; Labo Bio-medical Products B.V., Rijswijk, The Netherlands). This assay amplifies a small fragment of 65-bp from the L1 open reading frame and allows detection of a broad range of HPV genotypes.[13-15] HPV-DNA detection was performed by using an HPV DNA enzyme immunoassay (DEIA), which uses a defined cocktail of digoxigenin-labeled probes to detect a broad spectrum of HPV mucosal genotypes.

All HPV DNA-positive samples were genotyped subsequently with a line probe assay ($LiPA_{25}$) by reverse hybridization with type-specific probes for mucosal HPV genotypes 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68/73, 70, 74.[13] The LiPA strips were interpreted visually, using the standard reference guide. When samples tested positive using the DEIA, but showed no results on the LiPA strip, the SPF_{10} amplimer was analysed by direct sequence analysis with the BigDye Terminator cycle sequencing kit (Applied Biosystems, Nieuwerkerk a/d Ijssel, The Netherlands). The sequences were used as a query for screening of the sequences in the GenBank database (www.ncbi.nlm.nih.gov) with BLAST software.[16] HPV genotypes were assigned when a complete match between the 22-bp interprimer region and an HPV sequence in GenBank was found.

Genotypes not available on the LiPA strip and without a complete match in GenBank were considered HPV genotype 'X'. Low risk HPV (lrHPV) genotypes were defined as genotype 6, 11, 34, 40, 42, 43, 44, 54, 74, 89, 90 and 'X'. High risk HPV genotypes were defined as genotype 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. HPV genotypes 53, 66, 68, 69, 70 and 73 are nowadays classified as possible/probable high risk HPV (phrHPV) genotypes.[17] For analytical purposes, they were defined as hrHPV genotypes in this study. HPV genotypes 3, 12, 20 and 76 were identified as cutaneous genotypes. These HPV genotypes were regarded as contamination during sampling handling and were not taken into account in the calculation of HPV prevalence rates.

Questionnaire

All participants were asked to complete a questionnaire, which was divided in three parts. The first part existed of questions concerning sociodemographic characteristics (i.e. ethnicity, educational level, religion, and marital status). The second part asked for medical data, regarding both general (i.e. weight and length) and gynaecological health. The third part included questions on past and present sexual behaviour, to gain insight into risk factors for positive genital HPV status. Sexual contact was defined as oral, vaginal, or anal sex or genital contact.

The distribution of the questionnaires was preceded by a pilot study among eight volunteers to optimise the quality of the survey. Questionnaires could be filled in by using a digital (secured) system or via a paper version. All questionnaires were provided and saved with the unique study code.

Anogenital screening

Patients positive for either cutaneous type or mucosal type HPV were offered an anogenital screening visit at the outpatient clinic of the Department of Obstetrics & Gynaecology of one of the participating centres. Screening comprised an extensive inspection of the anogenital area and a smear of the cervix or vaginal vault in case of hysterectomy in the past. Cervical and vaginal cytology results are reported according to the Bethesda System. In case of any abnormal finding during this screening visit, patients were referred for further gynaecological examination (i.e. vulvar biopsy, colposcopy) and treatment according to local guidelines.

Patients with negative HPV-DNA test results were advised to have regular anogenital inspection and cervical cytology (performed by their own general practitioner), according to international guidelines.[18-20]

Data and statistical analysis

All data were pseudonymously stored in an electronic database for data collection and statistical analysis (IBM SPSS Statistics 20, New York, USA). For continuous variables, medians (range) or means (±SD) were calculated, depending on the distribution of the parameters. For categorical variables, total numbers and percentages were calculated for each modality. The modified Wald method was used to compute 95% confidence intervals (CI) for the HPV-prevalence. Missing answers were not included in the analysis.

The duration of immunosuppressive therapy was calculated as the time between date of transplantation and date of participation in the study. This variable was not calculated in patients with retransplantations since data on the use of immunosuppressive drugs after previous graft failure were not available.

We compared the prevalence of any-type of mucosal HPV between different groups of participants by means of crude risk ratio's (RR), estimated with log-binominal generalised linear models. To identify the variables that contributed independently to the risk of any-type mucosal HPV positivity, all variables that showed a significantly elevated RR in the univariable analysis were included in a multivariable analysis. Statistical significance was defined as a two sided P value $< 0{\cdot}05$.

Results

Participants

Study materials were sent to the 253 women who gave their informed consent; 218 (86.2%) returned the self-sample and were included in this study. See Figure 1 for an overview of study procedures.

Baseline

Table 1 shows baseline data of all included participants. Mean age at participation for this study was 55.4 years (SD 12.2) and women were on average 43.1 (SD 14.0) years of age at their first renal transplantation. The median duration of immunosuppressive therapy was 8.5 (range: 3.2-37.7) years. The majority of patients was treated with a calcineurin inhibitor (88% at time of transplantation; 67% at time of investigation). Induction therapy with antibodies against T-cells or the interleukin-2 receptor was used in a few patients only. Participants had a median BMI of 24.5 kg/m^2 (range: 16.8 – 48.3). The vast majority of participants (93%) did not smoke at the time of the study. None of the participants had been vaccinated against HPV prior to this investigation. There were no significant differences between responders and non-responders regarding both the mean age at participation (55.4 vs. 54.6 years, $P = 0.45$) and mean time since renal transplantation (12.4 vs. 12.2 years, $P = 0.77$).

Figure 1

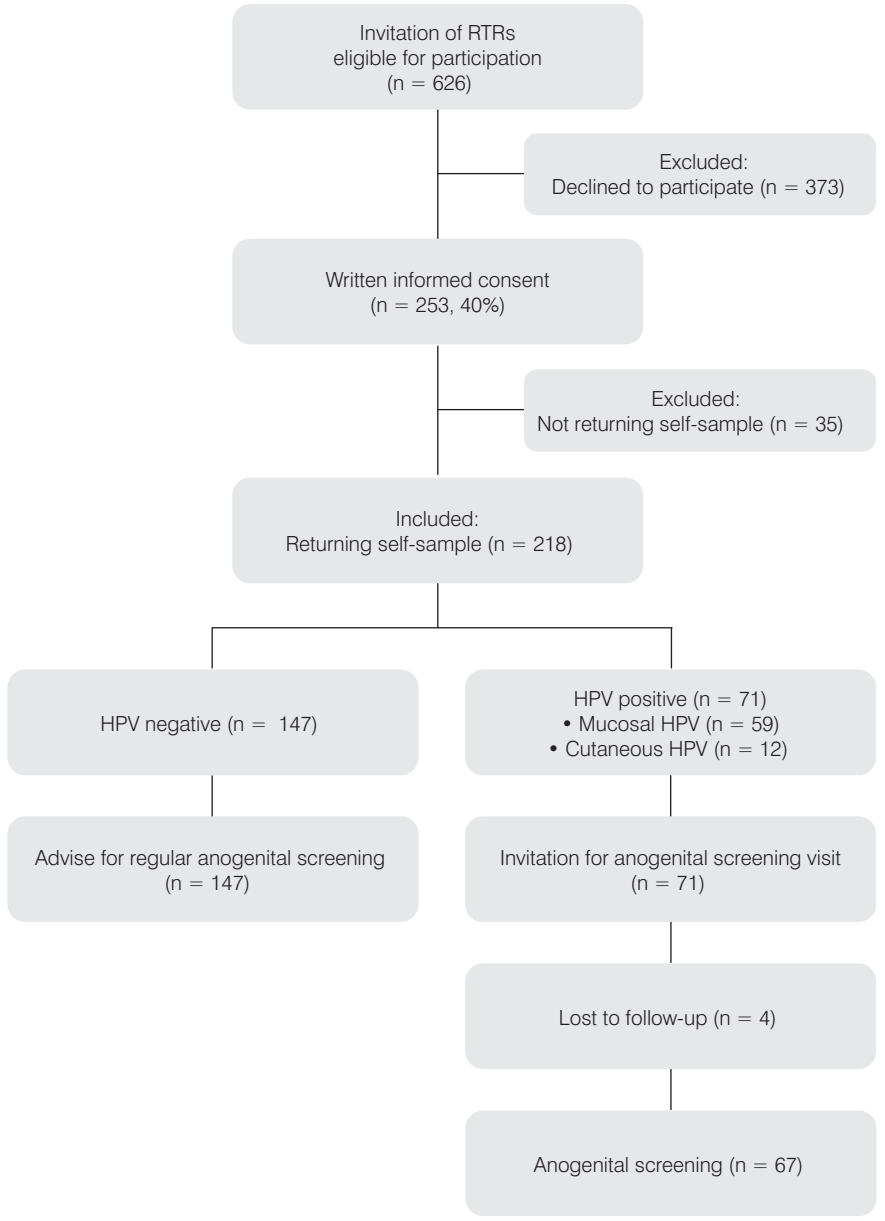

Table 1 Baseline data of participants

	Sample size (N)	
Age at study (years)	218	55.4 (SD12.2)
Age at transplantation (years)	218	43.1 (SD14.0)
Time on immunosuppression (years)	182	8.5 (3.2 – 37.7)
Time on dialysis (years)	218	1.7 (0 – 14.6)
Number of Tx	218	
1		182 (83.5%)
2		29 (13.3%)
≥3		7 (3.2%)
Current immunosuppressive therapy	218	
Mono		
Tac		49 (22.5%)
Mono-other		8 (3.7%)
Duo		
Ste-Tac		40 (18.3%)
Ste-Aza		37 (17.0%)
Ste-MMF		22 (10.1%)
MMF-Tac		18 (8.3%)
MMF-CsA		6 (2.8%)
Sir-other		12 (5.5%)
Duo-other		16 (7.3%)
Triple		
Sir-other		2 (0.9%)
Triple-other		8 (3.7%)
Creatinine (μmol/L)	218	113 (52 – 447)
Rejections (N)	218	
0		170 (78%)
1		30 (13.8%)
2-3		14 (6.4%)
>3		4 (1.8%)
BMI	211	
<18·5		8 (3.8%)
18·5 – 25		106 (50.2%)
>25		97 (46%)
Ethnicity	213	
Dutch / Other		203 (95.3%) / 10 (4.7%)
Current smoking	213	
Yes / No		15 (7%) / 198 (93%)
Education	213	
Primary / No education		20 (9.4%)
Lower secondary / Lower vocational training		99 (46.5%)
Higher secondary / Vocational training		58 (27.2)
Higher vocational training / University		36 (16.9%)

Table 1 Continued

	Sample size (N)	
Cause of ESRD	218	
Chronic glomerulonephritis		36 (16.5%)
Pyelonephritis		18 (8.3%)
Diabetic nephropathy		7 (3.2%)
Nephrosclerosis		9 (4.1%)
Polycystic renal disease		42 (19.3%)
Other		106 (48.6%)

Data are reflected as means (±SD) or medians (range).
N = Number; Tx = Transplantation; Ste = Corticosteroids; MMF = Mycophenolate mofetil; Tac = Tacrolimus; CsA = Cyclosporine A; Sir = Sirolimus; Aza = Azathioprine; BMI = Body Mass Index; ESDR = End stage renal disease

An overview of sexual behaviour of included women is given in Table 2. The majority of women was married or living together (74%) and almost all women had been sexually active (95%), mostly with male sex partners (98%). About half of the women (49%) had no sexual contact during the last six months preceding the study.

Twenty-six women (12%) underwent hysterectomy before the study. Participant-reported data on the performance of cytological cervical screening were available in 184 (96%) of the remaining subjects and showed that on average 2.6 (SD 2.0) cervical smears were performed during the last five years preceding entry into this study. Twenty-two percent of the women reported to have undergone at least one smear per year, 24% reported one smear in five years and 12% underwent no cervical screening at all.

HPV data

Of the 218 samples analysed, 59 (27.1%, CI 21.6-33.3%) tested positive for one or more mucosal HPV genotypes. The overall prevalence of lrHPV genotypes in our study cohort was 9.6% (CI 6.3-14.3%, $n = 21$) and hrHPV genotype prevalence was 17.4% (CI 12.9-23.1%, $n = 38$).

Table 3 shows an overview of any-type mucosal HPV prevalence and risk ratios for HPV prevalence between various subgroups of participants. Factors associated with an elevated risk on any-type mucosal HPV, according to the univariable analysis, were: transplantation in MUMC, younger age at study, non-Dutch ethnicity, younger age at transplantation, not being married, younger age at first intercourse, higher number of lifetime sexual partners, and higher number of sexual partners during the last six months. Time on immunosuppressive medication and the type of immuno-suppressive treatment were not related to HPV prevalence.

Table 2 Sexual behaviour

	Sample size (N)	Total cohort
Relationship	213	
Married		143 (67.1%)
Living together		15 (7.0%)
Widowed / Divorced		18 (8.5%)
LAT		8 (3.8%)
Single		29 (13.6%)
Sexual activity ever	209	
Yes		198 (94.7%)
No		11 (5.3%)
Age at first intercourse (years)	198	18 (11 – 58)
Ever diagnosed with STI	196	
Yes		16 (8.2%)
No		180 (91.8%)
Gender sex partner	195	
Male		192 (98.5%)
Female		1 (0.5%)
Both		2 (1.0%)
Lifetime sex partners (N)	186	
1		82 (44.1%)
2-5		82(44.1%)
6-10		16 (8.6%)
>10		6 (3.2%)
Sex partners last 6 months (N)	196	
0		97 (49.5%)
1		93 (47.4%)
2		3 (1.5%)
>2		3 (1.5%)
Sexual contact last 6 months	197	
Never		97 (49.2%)
Monthly		56 (28.4%)
Weekly		43 (21.8%)
Daily		1 (0.5%)

LAT = Living apart together; N = Number; STI = Sexually transmitted infection

Table 3 Overview of mucosal human papilloma virus prevalence and risk ratio's for specific categories of renal transplant recipients

			Univariable analyses				Multivariable analysis (N = 184)		
	Sample size (N)	HPV + (N, %)	Crude RR	95% C.I.	General P	P	Adjusted RR	95% C.I.	General P
Centre	218				**0.014***				**0.02***
UMCN	146	32 (21.9%)	1				1		
MUMC	72	27 (37.5%)	1.71	1.12-2.62		**0.014 ***	1.60	1.08-2.36	
Age at study (years)	218				**0.032***				0.62
≥ 60	83	15 (18.1%)	1				1		
40 – 59	109	33 (30.3%)	1.68	0.98-2.87		0·06	1.31	0.76-2.23	
≤ 39	26	11 (42.3%)	2.34	1.23-4.45		**0.009 ***	1.28	0.63-2.63	
Current smoking	213				0.21				
No	198	52 (26.3%)	1						
Yes	15	6 (40%)	1.52	0.79-2.95		0.21			
BMI	211				0.06				
<18·5	8	4 (50%)	1						
18·5 – 25	106	33 (31.1%)	0.62	0.30-1.32		0.23			
>25	97	20 (20.6%)	0.41	0.19-0.91		**0.030***			
Ethnicity	213				**0.003***				0.10
Dutch	203	52 (25.6%)	1				1		
Other	10	6 (60.0%)	2.34	1.34-4.09		**0.003 ***	1.52	0.92-2.53	
Age at transplantation (years)	218				**0.007***				0.18
<18	11	6 (54.5%)	1				1		
18-30	32	13 (40.6%)	0.75	0.38-1.48		0.40	1.18	0.65-2.15	
30-45	68	20 (29.4%)	0.54	0.28-1.03		0.06	0.75	0.41-1.38	
>45	107	20 (18.7%)	0.34	0.18-0.67		**0.002***	0.74	0.38-1.44	
Duration of immunosuppression (years)	182				0.56				
0-4.9	41	9 (22.0%)	1						
5-9.9	61	20 (32.8%)	1.49	0.76-2.95		0.25			
10-14.9	38	7 (18.4%)	0.84	0.35-2.03		0.70			
15-19.9	26	7 (26.9%)	1.23	0.52-2.89		0.64			
≥ 20	16	5 (31.2%)	1.42	0.56-3.60		0.46			

Table 3 Overview of mucosal human papilloma virus prevalence and risk ratio's for specific categories of renal transplant recipients

			Univariable analyses				Multivariable analysis (N = 184)		
	Sample size (N)	HPV + (N, %)	Crude RR	95% C.I.	General P	P	Adjusted RR	95% C.I.	General P
Rejection	218				0.45				
No	170	44 (25.9%)	1						
Yes	48	15 (31.2%)	1.21	0.74-1.97		0.45			
Number of Tx	218				0·08				
1	182	48 (26.4%)	1						
2	29	7 (24.1%)	0.92	0.46-1.82		0.80			
≥3	7	4 (57.1%)	2.17	1.09-4.30		**0.027***			
Cause of ESRD	218				0·26				
Chronic glomerulonephritis	36	13 (36.1%)	1						
Pyelonephritis	18	2 (11·1%)	0.31	0.08-1.22		0.09			
Diabetic nephropathy	7	3 (42.9%)	1.19	0.46-3.10		0.73			
Nephrosclerosis	9	4 (44.4%)	1.23	0.53-2.88		0.63			
Polycystic renal disease	42	9 (21.4%)	0.59	0.29-1.22		0.16			
Other	106	28 (26.4%)	0.73	0.43-1.25		0.26			
Current Immunosuppressive therapy	218								
Number of drugs					0.83				
1-2	208	56 (26.9%)	1						
3-4	10	3 (30.0%)	1.11	0.42-2.95					
Calcineurin inhibitor [Tac/CsA]					0.81				
Yes	145	40 (27.6%)	1						
No	73	19 (26.0%)	0.94	0.59-1.51					
Corticosteroids					0.71				
Yes	119	31 (26.1%)	1						
No	99	28 (28.3%)	1.09	0.70-1.68					
Proliferation inhibitor [AZA/MMF]					0.75				
Yes	111	29 (26.1%)	1						
No	107	30 (28.0%)	1.07	0.69-1.66					
Relationship	213				**0.001***				0.40
Married	143	29 (20.3%)	1				1		
Unmarried	70	29 (41.4%)	2.04	1.33-3.13			1.23	0.77-1.94	
Age at first intercourse	209				**0.035***				0.77
≥ 20	64	12 (18.8%)	1				1		
17-19	90	27 (30.0%)	1.60	0.88-2.92		0.12	1.17	0.66-2.05	
14-16	41	16 (39.0%)	2.08	1.10-3.94		**0.024***	1.34	0.74-2.43	
≤ 13	3	2 (66.7%)	3.56	1.38-9.18		**0.009***	1.34	0.69-2.60	
Never	11	1 (9.1%)	0.49	0.07-3.36		0.46	N/A		
Gender sex partner	195				0.74				
Male	192	55 (28.6%)	1						
Female	1	0	N/A	-					
Both	2	1 (50.0%)	1.75	0.43-7.11		0.44			
Lifetime sex partners	186				**<0.0001***				**0.001***
1	82	9 (11.0%)	1				1		
2-5	82	29 (35.4%)	3.22	1.63-6.38		**0.001***	2.63	1.37-5.06	
6-10	16	13 (81.2%)	7.40	3.83-14.32		**<0.0001***	4.45	2.13-9.32	
>10	6	5 (83.3%)	7.59	3.72-15.49		**<0.0001***	4.61	1.96-10.9	
Sex partners last 6M	196				**<0.0001***				0.47
0-1	190	52 (27.4%)	1				1		
≥2	6	5 (83.3%)	3.05	1.99-4.66		**<0.0001***	1.28	0.66-2.45	
Sexual contact last 6M	197				0.59				
Never	97	25 (25.8%)	1						
Monthly	56	16 (28.6%)	1.11	0.65-1.89		0.71			
Daily / Weekly	44	15 (34.1%)	1.32	0.78-2.25		0.30			

* = Significant at level 0·05

N = Number; RR = Risk ratio; C.I. = Confidence interval; Tx = Transplantation; ESDR = End stage renal disease; Ste = Corticosteroids; MMF = Mycophenolate mofetil; Tac = Tacrolimus; CsA = Cyclosporine A; Aza = Azathioprine; BMI = Body Mass Index; LAT = Living apart together; N/A = Not applicable; M = Months

Table 4 Human papillomavirus type-specific prevalence

		Prevalence	
	N	%	95% C.I.
Total hrHPV #	**38**	**17.4**	**12.9 – 23.1**
hrHPV genotype *			
16	9	4.1	2.1 – 7.8
18	2	0.9	0.0 – 3.5
31	4	1.8	0.6 – 4.8
35	2	0.9	0.0 – 3.5
39	2	0.9	0.0 – 3.5
51	9	4.1	2.1 – 7.8
52	5	2.3	0.8 – 5.4
53	5	2.3	0.8 – 5.4
56	2	0.9	0.0 – 3.5
58	1	0.5	0.0 – 2.8
59	3	1.4	0.3 – 4.2
66	7	3.2	1.4 – 6.6
68	2	0.9	0.0 – 3.5
69	1	0.5	0.0 – 2.8
Total lrHPV #	**21**	**9.6**	**6.3 – 14.3**
lrHPV genotype *			
6	2	0.9	0.0 – 3.5
11	1	0.5	0.0 – 2.8
34	2	0.9	0.0 – 3.5
40	1	0.5	0.0 – 2.8
42	3	1.4	0.3 – 4.2
44	1	0.5	0.0 – 2.8
54	3	1.4	0.3 – 4.2
74	3	1.4	0.3 – 4.2
89	1	0.5	0.0 – 2.8
90	1	0.5	0.0 – 2.8
X	13	6.0	3.4 – 10.0

= Total number of patients positive for HPV
* = Total number of different HPV genotypes detected. Percentages are calculated over total study population (n = 218). Multiple genotypes per patient do occur.
C.I. = Confidence interval; hrHPV = High-risk HPV; lrHPV = Low-risk HPV; N = Number

Additional univariable analyses on different anti-rejection therapies showed no significant risk-ratio's for the different modalities of rejection therapy (lymphocytic depleting agents, pulse steroids, or both; P = 0.92). However, the power of this test was low due to small study numbers and the results should be interpreted with caution.

Multivariable analysis with all variables that significantly contributed to an elevated risk on any-type mucosal HPV in the univariable analyses showed transplantation in MUMC and a higher number of lifetime sexual partners as factors that were independently associated with a raised risk of being mucosal HPV positive. Similar analyses on contributors to hrHPV infections showed no independent factors predicting a high-risk HPV positive state (detailed data not shown).

Specific HPV genotypes

In 43 of the 59 women positive for mucosal HPV (72.9%), a single HPV genotype was found. Sixteen women (27.1%) were found to have multiple genotypes. Table 4 shows the type-specific prevalence of all HPV genotypes identified. High-risk genotypes HPV 16 (*n* = 9, 4.1%), 51 (*n* = 9, 4.1%), and 66 (*n* = 7, 3.1%) showed the highest prevalence rates. In 13 samples (6%) the exact genotype could not be specified and was labelled genotype X. In one woman who reported to never having had sexual contact with another person, lrHPV genotype X was found.

Anogenital screening and follow-up

A total number of 67 of the 71 HPV positive patients (mucosal or cutaneous type) underwent anogenital screening. Table 5 summarises the screening results. Five patients were newly diagnosed with a high-grade squamous intraepithelial lesion (HSIL) and two patients were diagnosed with usual vulvar intraepithelial neoplasia (uVIN). Prior anogenital screening was not performed in these seven patients. Condylomata acuminata (caused by lrHPV) was diagnosed in two patients. Follow-up data of HPV-positive patients are shown in table 5. Mean follow-up was 20 months (SD 5), with a minimum of one year. Nine patients who were positive for hrHPV developed relevant cervical pathology during follow-up. One patient with uVIN developed severe anal intraepithelial neoplasia and one patient positive for lrHPV was diagnosed with anal carcinoma in situ during follow-up. 25 Of the 67 initially screened HPV-positive patients (37%) had no follow-up screening cytology. Initial screening results of these 25 patients were within normal limits.

Table 5 Screening results of Human papillomavirus positive patients

	Screening results			History	Follow up		
	N	Cytology*	Other		N	Cytology*	Other
Cutaneous types (n=12)	12	WNL	verruca plana (n=2)		10 2	WNL No follow up data	
Low risk mucosal types (n=21)	1	Lost			1	Lost	
	18	WNL		morbus Bowen (n=1) moderate/severe cervical dysplasia (n=1)	8 10	WNL No follow up data	anal carcinoma in situ (n=1)
	2	ASC-US			2	ASC-US	
High risk mucosal types (n=38)	3	Lost			3	Lost	
	20	WNL		LSIL / HSIL (n=5)	6 1 13	WNL ASC-US No follow up data	
	5	ASC-US	condylomata (n=1) usual VIN (n=1)		1 1 1 2	WNL ASC-US LSIL HSIL	moderate cervical dysplasia (n=1) severe cervical dysplasia (n=1)
	4	LSIL	usual VIN (n=1)	mild/moderate cervical dysplasia (n=1) mild cervical dysplasia (n=1)	2 2	LSIL HSIL	mild cervical dysplasia (n=1) severe cervical dysplasia (n=1)
	6	HSIL	condylomata (n=1)	mild - severe cervical dysplasia (n=1)	1 2 3	ASC-US LSIL HSIL	severe anal intraepithelial dysplasia (n=1) moderate cervical dysplasia (n=1) severe cervical dysplasia (n=4)

* = Bethesda 2001 classification; N = Number; Lost = Lost to follow up; WNL = Within normal limits; ASC-US = Atypical squamous cells with unknown significance; LSIL = Low-grade squamous intraepithelial lesion; HSIL = High-grade squamous intraepithelial lesion (HSIL)

Discussion

Our study describes the genotype-specific HPV prevalence in the largest cohort of female RTRs until now (*n* = 218). The overall prevalence of mucosal HPV infections was 27.1% and 17.4% for hrHPV in particular. The studied cohort showed a broad range of HPV genotypes and multiple HPV genotypes were found in 27.1% of HPV-positive patients. Based on the HPV testing and subsequent diagnostic follow-up, seven participants with occult premalignant anogenital lesions were identified. During a mean follow-up of 20 months even more relevant lesions were detected.

The HPV prevalence in the West-European general female population aged 45-55 years (corresponding to the average age of our participants) is 9-10%.[21,22] Our cohort of female RTRs showed an elevated overall HPV prevalence of 27.1% which is even higher than the prevalence rate of about 25% that was found with the same detection method in women of the general population aged 18-29 years.[22,23] Our findings differ from the results of two relatively small studies (*n* = 24 and *n* = 60, respectively) showing similar frequencies of HPV positivity in female RTRs compared to controls. [7,8] Notably, the prevalence in the control groups of these studies was rather high when compared to European data of the general population.

The increased HPV prevalence in our study cohort may be related to acquiring more new infections, delayed clearance of infections, or an increased reactivation of latent HPV infections. Our cohort of patients had a limited mean number of recent sexual partners and sexual abstinence during the last six months in about 50% of the participants. Therefore, the most plausible explanation for the high HPV prevalence is

delayed clearance and reactivation of latent infections due to the immunosuppressed state.[24,25]

Somewhat surprising, the duration of immunosuppressive treatment and the occurrence of an acute rejection with subsequent intensifying of immunosuppressive therapy, were in this cohort not related to the risk of HPV positivity. This suggests that the current intensity of immunosuppression may be more important than the cumulative exposure.

A higher number of lifetime sexual partners was independently associated with HPV positivity. This is in concordance with previous epidemiological data showing that total number of sexual partners is one of the most dominant risk factors for HPV positivity.[23] We have no clear explanation for the difference in HPV prevalence rates between the two participating centres.

Of the studied cohort, 7.3% showed infection with multiple HPV genotypes (27.1% of all mucosal HPV positive RTRs). These percentages are comparable with percentages of the general Dutch population aged 18-29 years.[23] Former studies described having multiple HPV infections as a risk factor for hrHPV persistence.[26,27] Multiple infections may increase the overall viral load which may overcome immune control. It can be speculated that this risk is even stronger in immunocompromised patients.

Worldwide, the five most prevalent HPV genotypes in women with normal cytology are 16 (2.3-3.2%), 18 (0.8-1.4%), 31 (0.8%), 52 (0.6-0.9%), and 58 (0.7%).[21,22] We found a very broad spectrum of 24 individual HPV genotypes among our cohort of female RTRs enclosing seventeen patients with abnormal cytology. The five most common genotypes were somewhat different compared to the general population: 16 (4.1%), 51(4.1%), 66 (3.2%), 52 (2.3%), and 53 (2.3%) prevailed. The genotypes 18, 31, and 58 were less prevalent in our cohort. Besides, genotype 16 did not predominate over other HPV genotypes to the same extent as seen in the general population. A similar shift towards other HPV genotypes has been observed in HIV-infected patients. [28] It was previously shown that the association between CD4-cell counts and risk of infection is weaker for HPV16 than for other genotypes.[28] This suggests that the prevalence of HPV16 is relatively independent of the immune status.

Mucosal HPV-DNA, including high-risk HPV genotypes, has been repeatedly detected in a proportion of extra-genital NMSC. However, whether HPV plays a causal role in the oncogenesis of NMSC is still a matter of debate.[29-31] Having NMSC on extra-genital skin was not registered in our current study. However, from previous work we know that the development of NMSC and gynaecological (pre)malignancies are not related to each other.[4]

Prophylactic vaccines against hrHPV genotype 16 and 18 are highly effective for the prevention of persistent infections and anogenital cancer. It is attractive to speculate on the beneficial effect of this vaccine in transplant recipients. However, recent data showed suboptimal immunogenicity of the quadrivalent HPV vaccine in

transplant patients on immunosuppressive therapy.[32] Pre-transplantation vaccination may be more beneficial and further studies are going on in this area.

Overall, the women included in our study had limited knowledge about their elevated risk on HPV and HPV-related lesions. Besides, intensified cervical screening was not performed on a regular basis in a considerable number of participants. This might explain the finding of seven occult cervical/vulval lesions by anogenital screening of HPV positive study participants. Although patients were extensively verbally advised to have yearly follow-up after initial screening, a large part of patients was lost to follow-up. This was particularly true in patients with known positivity for high-risk HPV genotypes, where 13/35 patients were lost to follow-up. Notably, most of the high-risk HPV positive patients had abnormal cytology at follow-up visit and some patients showed progression of disease, underscoring the specific value of screening in this population. Based on these findings, we see a strong need for improvement of gynaecological follow-up in the transplant patients. Therefore, we are currently preparing a qualitative study assessing the barriers and facilitators for anogenital screening in both female RTRs and professional health care givers. We aim to find reasons for non-attendance and, subsequently, will develop a strategy to improve the attendance at annual anogenital screening. Possibly, education of immunocompromised patients and involved professionals about the obviously elevated risk for HPV-related anogenital malignancies and the consequent need for cervical screening is important. In women who are reluctant to undergo cervical screening by a physician or nurse, self-sampling for hrHPV testing may be a valuable alternative. Moreover, attention for other preventive strategies like vaccination and appreciation of pre-transplant HPV-related lesions is warranted.

Some limitations of this study need to be acknowledged. Due to the cross-sectional design, we have no data on the dynamics of HPV infections and the concurrent prevalence of genotypes over time, which might have provided more insight into the relationship with the intensity and type of immunosuppression. Furthermore, since only 40% of the invited female RTRs consented to participate, we cannot exclude some form of response bias. Possibly, either patients with regular anogenital screening or patients with known anogenital pathology opted to withdraw from this study. Finally, the possible use of immunosuppressive drugs before transplantation was not known, which made the data of total duration of immunosuppression slightly less accurate.

To investigate the epidemiology of HPV-infections in this cohort of immuno-compromised female patients, the highly sensitive SPF_{10}-LiPA PCR was used. It may be argued that, due to its low threshold values, this test cannot discriminate between active and latent infections, and has therefore a lower specificity for clinically relevant infections. However, in contrast to the recently shown lower pooled sensitivity of HPV-testing on self-collected samples for detecting CIN2 or worse compared to

testing on a clinician based sample, SPF_{10}-LiPA PCR based hrHPV detection on self-collected samples approaches the sensitivity and specificity of clinician-taken samples.[9,33,34] Therefore, using the SPF_{10}-LiPA PCR seems a valuable strategy in HPV-based screening on self-collected specimens.

In conclusion, the results of this observational, epidemiological study among a relatively large cohort of female RTRs show a high prevalence of HPV positivity with a shift in the distribution of genotypes as compared with the general population. Use of a self-sampling method for HPV positivity can help in early detection of (pre) malignant anogenital lesions which are more frequent in this population. Where this study focused on the point-prevalence of HPV infections after transplantation, we are currently performing a prospective follow-up study to provide knowledge about the course of HPV infections before and after transplantation. This may contribute to strategies for the prevention of anogenital (pre)malignancies in the vulnerable population of RTRs.

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CHAPTER

9

General discussion

In the present thesis, several clinical studies on genital psoriasis and genital (pre) malignancies in female renal transplant recipients (RTRs) have been described. This thesis hereby provides more insight into these highly relevant, but frequently hidden, problems in the genital region.

The current chapter provides a general discussion of the themes that are presented in this thesis and describes the main conclusions in accordance with the aims as defined in chapter 1. Subsequently, implications for daily clinical practice will be highlighted. Finally, future suggestions for a multidisciplinary approach of the genital diseases as described in this thesis will be given.

Discussion of study data

In psoriatic patients, genital involvement is frequently occurring in both males and females of all ages. Percentages of psoriatic patients who have significant genital problems during the course of their disease vary from at least 16.5% up to 46% (chapter 2 of the present thesis).[1-5]

Genital psoriasis has been erroneously classified as flexural psoriasis, both in the literature as in daily dermatological practice. This thesis (chapter 2) shows that 38% of patients with genital psoriasis have no flexural psoriasis. Therefore, genital lesions are frequently missed when flexural skin (i.e. inguinal skin) is not affected with psoriasis and genital skin is neglected during physical examination.

As outlined in chapter 3, the quality of life and sexual health are diminished in a considerable number of male and female patients with psoriasis. Especially women experience high levels of sexual dysfunction (48.7%) and, in the presence of genital lesions, also high levels of sexual distress (50.8%). Therefore, health care professionals cannot ignore the major impact of genital psoriasis on (sexual) quality of life and need to pay attention to the consequences of involvement of the genital skin. The major impact on sexual health of other genital skin diseases, such as lichen sclerosus, is also well known and paid attention to.[6,7]

The quality of life indices that are frequently used for patients with psoriasis and other dermatoses, only sparsely cover the domain sexual function. The generic questionnaires SF-36 and EQ-5D do not mention sexual health at all, and in the disease specific DLQI the domain is restricted to one short question. The Skindex-questionnaire only questions about sexual health in the long version of the questionnaire; the frequently used short 16-item Skindex only mentions the term ‘close relations’. Therefore, these commonly used questionnaires will probably not provide an adequate estimation of the actual impact of (genital) psoriasis and other skin diseases on sexual health.

When reconciling the frequency of genital psoriasis from the literature, it is of eminent importance that professionals actively ask for the existence of genital lesions and inspect the genital area in patients with psoriasis. Although, as presented in chapter 4 of this thesis, the vast majority of patients with genital psoriasis experiences significant discomfort such as itch, pain or a burning sensation, it turns out that about half of the patients does not discuss their complaints with their physician. Moreover, over two thirds of patients never receive treatment for genital psoriasis. Among this last group of patients, 20-40% is classified as having 'severe symptoms'. The fact that physical examinations during standard dermatological consultations are practically always restricted to extra-genital skin and patients mostly keep wearing their underwear may explain this impressive unmet medical need. Chapter 5 shows that adequate diagnosis and treatment of genital lesions with attention for the possible impact on (sexual) quality of life has a significant impact on disease severity and quality of life within limited time exposure. Therefore, an active approach for possible genital psoriasis including inspection of the genital skin without any restraint is warranted.

As a result of chronic use of immunosuppressive medication, RTRs have a significantly raised risk for the development of HPV-related (ano)genital (pre)malignancies compared with the general population.[8-13] Chapter 6 of the current thesis confirmed this elevated risk, which appears to be twofold to sixfold for CIN, threefold to sixfold for cervical carcinoma, 45-50-fold for vulvar carcinoma and about 10-fold for anal cancer in RTRs. Recent data illustrate an elevated risk of solid organ recipients for vaginal (11-fold), vulvar (20-fold) and anal intraepithelial neoplasia (12-fold) as well.[14] Remarkably, cervical cancer showed no elevated incidence in that publication, which was attributed to effective cytological screening of the studied population.[14]

It is known that the risk of progression of low-grade lesions toward high-grade lesions among immunocompromised patients may be considerable higher and the development may be exceedingly rapid in comparison with immunocompetent individuals.[15,16] So, besides their elevated risk for HPV related anogenital lesions, female RTRs may be at higher risk for higher grade disease compared to immuno-competent individuals.[17]

Parallel to vulvar (pre)malignancies, there is evidence for an HPV-mediated and a non-HPV-mediated pathway in penile intraepithelial neoplasia (PIN) and penile cancer.[18] The risk for HPV-related PIN and penile cancer is also known to be evidently elevated in male organ transplant recipients (SIRs 4-19).[8,14] To date, unfortunately, little is known about HPV infections in male transplant recipients and more detailed knowledge on this theme is needed.

Based on the elevated risk for anogenital (pre)malignancies in female RTRs, yearly anogenital screening is broadly advised although there is no strict evidence

that this policy of intensified screening will lead to decreased morbidity and mortality.[19-21] Chapters 6 – 8 show that the uptake of intensified (ano)genital screening among the female renal transplant population is low and that many female RTRs have suboptimal cervical screening after their transplantation. This finding is in accordance with previous studies among female RTRs.[22,23] Probably, both patients and healthcare professionals focus on the preservation of renal function. However, implementation of intensified anogenital screening and monitoring for potential lethal, though preventable, malignancies of the genital tract may have great benefits.

High-risk HPV has a major role in the development of genital (pre)malignancies. By using a self-sampling method, we show in chapter 8 of this thesis that female RTRs have an obviously elevated HPV point-prevalence compared to the general population (27%, vs. 9-10% in the general population). Moreover, there appears to be a shift in the distribution of HPV genotypes in female RTRs as compared to the general population. Both chapter 7 and 8 of this thesis describe that female RTRs may be infected with a broad pallet of HPV genotypes, including less common hrHPV genotypes (e.g. genotype 51 and 66). Interesting, chapter 7 shows that in case of multifocal lesions, frequently different HPV genotypes are present at different locations. These findings illustrate that immunocompromised RTRs are target for repeated and independent infections with various types of HPV.

Screening through self-sampling of 67 HPV-positive RTRs at our outpatient clinic revealed about 10% of female RTRs with occult premalignant genital lesions that in the long term would have progressed towards invasive lesions (chapter 8). This indicates that HPV self-sampling may be very helpful in early detection of (pre) malignant anogenital lesions in the vulnerable renal transplant population.

Major conclusions

PART A: Genital psoriasis

1. The genital area is involved in up to 46% of patients with psoriasis. Flexural and genital psoriasis should be regarded as distinct manifestations.
2. Quality of life and sexual health are considerably diminished in patients with psoriasis. Particularly women with genital psoriasis have high levels of sexual distress. Current scoring systems for quality of life in psoriasis do not sufficiently comprise the impact of (genital) psoriasis on sexual health.
3. Although numerous patients report a significant burden of disease, the consultation rate for genital psoriasis is low and examination of genital skin is frequently lacking.
4. Adequate management of genital psoriasis leads to significant improvement of disease severity and (sexual) quality of life within limited time investment.

Part B: HPV-related genital (pre)malignancies in female renal transplant patients

1. Cervical screening of female RTRs is not performed in accordance with the advised yearly intervals.
2. The risk for female RTRs to develop genital (pre)malignancies is obviously increased compared to women in the general population.
3. HPV plays a crucial role in the development of (ano)genital (pre)malignancies in female RTRs. Multifocal lesions within female RTRs frequently contain different hrHPV genotypes in both lesions.
4. The prevalence of mucosal HPV infections in female RTRs is high, with a broad range of HPV genotypes. HPV-based screening on self-collected specimens is an adequate method to detect female RTRs with genital (pre)malignant lesions.

Implications for daily clinical practice

The current thesis underlines the need for more attention for the wide range of benign and (pre)malignant genital skin conditions that are highly prevalent but frequently missed in daily clinical practice. The prevalence, unmet medical need and psychosocial impact of these lesions are likely to be underestimated.

Unmet medical need with respect to diagnosis and care for patients with genital psoriasis

The genital skin is involved in 16-46% of psoriatic patients and a considerable number of patients experience diminished (sexual) quality of life. Therefore, more attention for genital psoriasis and its implications has to be developed by healthcare professionals.

As an adequate diagnosis is the first step in the care for patients with genital psoriasis, inspection of the genital area should be performed in each new patient and in patients with genital complaints. A specialised clinic for genital diseases with attention for adequate diagnosis, treatment and impact on (sexual) quality of life proves worthwhile in chapter 5 of this thesis. In particular, the first two consultations, with an interval of approximately six weeks, prove to be crucial to reach a significant improvement of the genital skin disease and its impact. Thereafter, a plateau is reached. This illustrates that it is worthwhile to invest time by a healthcare professional with knowledge and skills to support patients with genital psoriasis during the first consultations.

Literature on therapy with respect to genital psoriasis has its limitations as the discrimination between flexural and genital psoriasis is often not made and randomised controlled trials on the efficacy and safety of investigated treatments for genital skin are sparsely available. Based on the available literature[24], the following

treatment paradigm is advised for genital psoriasis: start with weak corticosteroids and, in case of resistance to treatment, increase the potency of the corticosteroid preparation. Treatment with potent corticosteroids should be limited to a few weeks in view of their atrophic effects, particularly on genital skin. The addition of topical vitamin D analogues or coal tar preparations has been suggested to be effective. These can reduce the side-effects of corticosteroids, although irritation may restrict their application. Evidence for the use of calcineurin inhibitors on genital skin is scarce. These should be regarded as final treatment options. At our research outpatient clinic for genital psoriasis the above mentioned treatment approach proved to be effective.

Unmet medical need with respect to screening of genital (pre) malignancies in female RTRs

As the elevated risk to develop genital (pre)malignancies is established for female RTRs, attention for the recommended intensified screening is necessary. Wong et al. showed that the recommended policy of annual screening for cervical malignancies using conventional cytology in transplanted women seems to be cost-effective.[25] However, they compared annual screening with no screening at all. The Netherlands have, as many other countries, an organised cervical cancer screening programme since the early 1970s. In the Dutch programme, women aged between 30 and 60 years are invited for conventional cervical smears every 5 years. It would be interesting to compare the advised intensified annual screening with the standard organised Dutch screening programme for cost-effectiveness, but such a study will be hardly feasible. In addition to this, it has to be realised that in the near future screening strategies in the Netherlands will be changed towards primary hrHPV testing and additional triage for hrHPV-positive screening results. Besides, the impact of regular screening of female RTRs on reduction of vulvar (pre)malignancies still has to be demonstrated.

It is known that people with HIV/AIDS have an increased incidence of an extensive range of, particularly infection-related, cancers as well. The pattern of this increased cancer risk showed a striking similarity between people with HIV/AIDS and immuno-suppressed transplant recipients in a meta-analysis by Grulich and colleagues.[26] So, although the mechanisms are different, immune deficiency leads to increased cancer risk in both patient groups.

Recently, van der Zande and Ankum showed in a short literature review equal risks of cervical premalignancies among HIV-positive and HIV-negative women in case of repetitive negative cytology results or persistent negative hrHPV test results.[27] Therefore, they advocated extending the current yearly screening interval for HIV-positive women in these particular groups. It is attractive to speculate about a parallel with female RTRs, which pleads for further research.

To improve the attendance to cervical screening of women with an increased risk for cervical cancer, it has previously been shown that a personal invitation for cervical screening by a woman's own general practitioner achieves a higher screening rate compared to an invitation by a national call system through the local health authority.[28] Thus, to improve the cervical cancer screening of female RTRs in daily clinical practice, it seems reasonable to optimise the involvement of general practitioners in this screening. In the light of patient-centred care, a qualitative study involving both female RTRs and their physicians (both the nephrologists and general practitioners) may be suitable to explore ways to further improve anogenital screening of the high-risk transplant population.

Multidisciplinary approach and awareness

Because patients with genital lesions may consult different specialties, the question arises which professional will take the ultimate responsibility for those patients. In addition, when treating RTRs with genital (pre)malignant lesions, management decisions are complex because of the localisation of the donor kidney in the lower pelvis. Frequently, there is reluctance to reduce the immunosuppression to prevent progression of (pre)malignancies because of fear for graft loss. This illustrates the importance of a structured, multidisciplinary approach for genital skin lesions, combining the expertise of several medical specialists.

A dedicated, multidisciplinary approach for vulvar skin pathology is indeed invaluable: it improves the understanding of vulvar disease, the making of correct diagnoses and the prescription of optimal treatment. Besides, attending a multidisciplinary vulvar clinic is associated with a significant improvement in quality of life of patients.[29-32] Moreover, it may reduce the number of hospital visits for the patients, although further studies are needed to substantiate this statement. As a result, several multidisciplinary vulvar clinics arose worldwide. The Dutch Society for Vulvar Pathology is currently developing quality criteria for vulvar clinics, to preserve quality and high specialisation of these multidisciplinary clinics in the Netherlands.

Awareness of the major impact on (sexual) quality of life is absolutely needed when treating patients with both benign and (pre)malignant genital lesions. With a pro-active and patient centred approach, professionals may remove barriers and create a safe environment in which such a sensitive topic can be discussed. A short questionnaire that patients complete at home or in the waiting chambers may give a quick overview of pressing psychosexual issues.[33] In case of any impairment of (sexual) quality of life, a two-track policy seems the most appropriate way to tackle these problems. Medical treatment may diminish symptoms and, in addition, psychosexual therapy by a (dermato)psychologist or a (gynaeco)sexologist may ameliorate the coping behaviour with respect to genital skin disease.

The gynaecologist should ideally be involved in both pre- and post-transplantation

care. As described in chapter 6 of this thesis, we suggest that yearly screening may be postponed to approximately 3 years after RT under the condition that patients are screened for anogenital pathology and HPV-status before their RT. However, it is unknown from which moment on screening should be performed after RT. More awareness of the elevated risk for (ano)genital lesions among both immunocompromised patients as well as health care professionals is warranted. Bringing in the expertise of general physicians or nurse practitioners to counsel patients about their elevated risks may improve the screening rate of female RTRs.[34,35]

Future perspectives

Education of professionals

Adequate knowledge about genital skin disease is essential for good clinical practice. However, so far, only little attention for genital skin has been given in medical school and subsequent training to become a medical specialist. It is known that the majority of vulvovaginal experts are self-taught and have learned their expertise from courses and mentorship experiences rather than through a standardised curriculum.[36] In theory, all involved professionals should become more aware of the possibility of genital manifestations of general dermatological disorders like psoriasis or eczema. Moreover, knowledge about more specific genital dermatoses like lichen sclerosus or VIN is warranted. Recent initiatives to enlarge knowledge, like digital trainings with respect to genital skin disease, are promising and deserve a place in the training of young colleagues.

Education and subsequent increased knowledge about genital skin pathology among general physicians will probably yield into a more suitable treatment and, when indicated, referral of patients towards the appropriate medical specialists.

Instructions for self-management and the value of nurse practitioners

Instructions for self-management are indispensable for patients as described in this thesis; they may help to stimulate patients in personal decision making and improve clinical outcomes.[37] Therefore, we developed a brochure about genital psoriasis in association with the Dutch Psoriasis Society. In this way, information about genital psoriasis and its treatment is made easily accessible for patients. Even more, the possible emotional impact of genital psoriasis is acknowledged and possibilities for supportive care are mentioned. Chapter 5 of this thesis illustrates that invested time for instructions is indeed worthwhile.

It is attractive to speculate about the value of a specialised nurse practitioner in this particular field. Care provided by nurse practitioners may be preferable over care provided by medical specialists from a health economic perspective.[38] Nurse

practitioners are pre-eminently trained to enlarge self-management of patients. They may provide counselling about diagnosis, treatment, elevated risks, importance of regular screening and self-inspection of the genital area. In addition, they may provide consultations on sexual problems with a lower threshold compared to medical specialists.[39]

Guidelines and 'Treatment Goals' regarding genital psoriasis

The most recent Dutch guideline 'Psoriasis' dates from 2011 and does not discriminate between genital and flexural psoriasis. The treatment advises for genital lesions are completely integrated in the advice for the treatment of flexural psoriasis. Besides, there is no attention for the impact on sexual health and the value of a sexologist in the care for patients with (genital) psoriasis. Therefore, there may be room for implementation of the previously described treatment paradigm and attention for sexual health in the next Dutch guideline.

The significant impact of psoriasis on health related quality of life and the frequent undertreatment of patients with moderate-to-severe psoriasis have led to a European group to develop consensus on psoriasis treatment goals, aiming to achieve the most optimal treatment results.[40] It is clearly indicated that special clinical situations that may lead to a significantly impaired quality of life, may change mild psoriasis to moderate-to-severe disease that warrants more intense (systemic) treatment modalities. Involvement of genital skin is indicated as one of these situations by the European expert panel. So, based on the recently developed treatment goals, there may be room for systemic treatment in case of genital involvement although 'overall' psoriasis severity scores indicate only mild disease.[40] Unfortunately, the evidence for efficacy of these systemic treatments in genital psoriasis is very limited and further research in this respect is needed.

HPV self-sampling and triage of hrHPV positive cases

Participation in screening is the most important factor determining the success of screening. Various studies have shown that self-sampling increases the participation of non-responders in current cervical cancer screening programs.[41] As the ideal of yearly conventional cervical screening combined with anogenital inspection in female RTRs seems to be hardly feasible, it may be worthwhile to implement self-sampling as the primary screening tool for RTRs in the short term. Self-sampling is suitable for HPV-testing, has a high level of concordance with physician-collected samples and is highly accepted by women.[42-44] Moreover, self-sampling may reduce the doctor-density for female RTRs, as only subsequent triage for women who tested hrHPV positive is necessary. When HPV self-sampling indicates the female RTRs who are at risk for genital (pre)malignancies, it may stimulate the concerning high-risk patients to have subsequent cervical screening.

Up until now, it remains uncertain which triage strategy is the most optimal after the detection of hrHPV positive cases. It is critical that the follow-up and further management are acceptable to participants and therefore, triage strategies directly applied on self-collected material are ideal. DNA methylation marker analysis as a triage test directly applied on self-collected cervicovaginal material seems promising.[41] DNA methylation is an epigenetic process involving the addition of a methylgroup (CH_3) to DNA nucleotides. As a result, the DNA structure changes and the expression of genes is altered. Abnormal DNA methylation patterns are associated with malignant transformation. Currently, research is performed towards the development of specific DNA methylation markers which may be used as triage test for detecting ≥CIN3 in hrHPV positive cases.

Despite the promising future in the field of self-sampling and hrHPV based triage for secondary prevention of cervical cancer, it remains uncertain whether these tests also predict the presence of vulvar (pre)malignancies. It figures that vulvar lesions will infrequently be present in case of HPV negative cervicovaginal samples, although this is not confirmed by the present literature. For the time being, regular inspection of the genital skin for the detection of relevant cutaneous lesions remains important for the high-risk populations. However, the impact of this policy on reduction of vulvar (pre-)malignancies in RTRs remains to be demonstrated.

Vaccination

The quadrivalent (genotypes 6, 11, 16 and 18) and bivalent (genotypes 16 and 18) HPV vaccines have proven to be very safe with long-term durability of protection against primary infection with vaccine types and a moderate degree of cross-protection against some none-vaccine types in the general population.[45] Unfortunately, although the vaccine was safe and well tolerated, adult transplant recipients recently showed suboptimal immunogenicity of the quadrivalent HPV vaccine.[46] On the other hand, in a small study among adolescent transplant recipients, the immunogenicity to the quadrivalent HPV vaccine showed to be robust with seroconversion to all four HPV genotypes.[47] More clinical trials on the immunogenicity of the HPV vaccination and its potential to protect for HPV-related (pre)malignancies in immunocompromised transplant recipients are needed.

Currently, the efficacy of a broad spectrum vaccine, against nine HPV subtypes is being studied in Phase III studies. This vaccine includes the four HPV genotypes of the quadrivalent vaccine and five additional oncogenic HPV genotypes (31, 33, 45, 52, 58).[48] It would be interesting to know the effects of this nine-valent vaccine in transplant recipients, especially because they carry a broad range of HPV genotypes as we showed in chapter 8 of this thesis.

In the light of the possible benefit of vaccination for female RTRs, it is important to know whether and when RTRs become HPV positive after renal transplantation to

define the most appropriate moment of vaccination. Therefore, a prospective investigation towards HPV-infections before and after renal transplantation is currently conducted at our centre. Besides, further studies are advised to determine the optimal HPV vaccine genotypes, vaccination schedule and moment of vaccination (pre- or post-transplant) for prevention of genital neoplasia in organ transplant recipients. As vaccination against HPV will not provide 100% protection against genital (pre)malignancies, screening of the high-risk organ transplant population will remain important.

Conclusion

This thesis focuses on both benign and (pre)malignant genital skin lesions and shows that a multidisciplinary approach with attention for prevention, adequate diagnosis and treatment and for the impact of these lesions on (sexual) quality of life is of great importance. Genital psoriasis should be regarded as a separate manifestation of psoriasis with its own treatment paradigm and implications on (sexual) quality of life. Improvement of screening and prevention of HPV-related genital (pre)malignancies in female RTRs remains necessary and deserves further attention in the near future.

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CHAPTER

10

Summary & Samenvatting

Summary

This thesis includes clinical studies on genital psoriasis and HPV-related (pre) malignancies in female renal transplant recipients (RTRs).

The two main themes of this thesis are introduced in ***Chapter 1***. Based on an overview of the literature, current knowledge about epidemiology, clinical presentation, diagnosis and therapy of genital psoriasis is described in this chapter. Furthermore, it gives an introduction on renal transplantation, immunosuppressive therapy and post-transplant genital (pre)malignancies. At the end of *Chapter 1* therapeutic concessions that are frequently needed in female RTRs with genital (pre)malignancies and possible ways of prevention of these lesions in this immunocompromised population are reviewed.

Part A: Genital psoriasis

The prevalence and other epidemiological characteristics of genital psoriasis in the Netherlands are described in ***Chapter 2.*** Data collected by using self-administered questionnaires show that up to 46% of patients with psoriasis suffer from genital involvement during the course of their disease. Genital skin can become affected with psoriasis at any age. Furthermore, *Chapter 2* illustrates that 38% of patients with genital psoriasis do not have the flexural skin affected. From this study it is concluded that at least one third of patients with psoriasis suffer from genital lesions which are not associated with flexural psoriasis. Therefore, it is reasonable to assume that flexural and genital psoriasis are most probably distinct manifestations of psoriasis. More attention to the genital region of both male and female patients with psoriasis at any age is required.

In order to increase knowledge about quality of life and (attention for) sexual health in patients with genital psoriasis, these issues are studied among a large group of patients with genital psoriasis. The results are described in ***Chapter 3***. This chapter illustrates that patients with genital lesions have significantly worse quality of life compared to patients without genital lesions. Sexual health is diminished in a considerable number of patients with psoriasis and particularly women with genital lesions have high levels of sexual distress. This chapter underscores the need for physicians to pay attention to the impact of (genital) psoriasis on psychosocial and sexual health.

Chapter 4 focuses on the experiences of patients regarding the role of the physician in the treatment of genital psoriasis and the symptom intensity of these lesions. It shows that the vast majority of patients with genital psoriasis experiences significant discomfort whereas about half of them does not discuss their complaints with their

physician. In addition, *Chapter 4* illustrates that over two-thirds of patients never apply treatment for genital psoriasis lesions. All together, this chapter demonstrates that the consultation rate for genital lesions is low, while numerous patients report a significant burden of disease. An active and patient-centred approach to identify and treat patients with genital psoriasis is recommended.

It was aimed to assess the value of specialised care for patients with genital psoriasis in ***Chapter 5***. Therefore, patients with genital psoriasis were invited for treatment and support for at least one year at our specialised outpatient clinic with extensive attention for genital lesions and (psychosexual) quality of life. Both genital psoriasis severity and quality of life parameters improved significantly within the first follow-up period of approximately six weeks. In female patients, also the sexual health significantly improved. Based on the results described in *Chapter 5*, it is concluded that genital psoriasis can relatively easily be treated within limited time exposure, also resulting in significant improvement of quality of life. Routine attention for possible genital psoriasis and accompanying impact on (psychosexual) quality of life is advised.

Part B: HPV-related genital (pre)malignancies in female renal transplant recipients

Immunosuppressive therapy in RTRs is associated with an increased risk for the development of (pre)malignancies involving the female lower genital tract. Therefore, intensified genital screening is advised, although there is a lack of evidence for this policy. In ***Chapter 6*** it is presented that cervical screening is not performed yearly in a cohort of 224 female RTRs. Besides, the increased risk for female RTRs in this cohort to develop gynaecological (pre)malignancies is described: 2-6 fold for cervical intraepithelial neoplasia, 3-fold for cervical carcinoma and 50-fold for vulvar carcinoma. This chapter emphasises the need for more attention to both anogenital and cervical surveillance of female RTRs.

In ***Chapter 7***, an overview of female anogenital post-transplantation (pre)malignancies over a period of 40 years renal transplantation is given. Besides, the genotype-specific prevalence of HPV in these (pre)malignancies is studied. *Chapter 7* illustrates a high number of anogenital malignancies in female RTRs, nearly all caused by HPV. Interestingly, in case of multifocal lesions within one patient, frequently different high-risk HPV genotypes are identified at different locations. This demonstrates that immunocompromised RTRs are target for repeated and independent infections with various types of HPV. *Chapter 7* underlines the importance of anogenital screening and monitoring before and periodically after renal transplantation.

As immunosuppressive treatment is clearly associated with an increase in the occurrence of HPV-related genital (pre)malignancies, ***Chapter 8*** addresses the genotype-specific prevalence of HPV infections in a large cohort of female RTRs. By analysing self-collected cervicovaginal samples, this chapter reflects an overall prevalence of mucosal HPV infections of 27.1% and 17.4% for high-risk HPV genotypes in particular. This is high compared to the age-matched West-European population. Besides, *Chapter 8* shows a shift in the distribution of HPV genotypes as compared with the general population. By offering anogenital screening to all HPV positive participants, this study identifies a substantial number of female RTRs with occult genital premalignancies. We believe that the introduction of self-sampling for HPV-positivity can help in early detection of (pre)malignant anogenital lesions in RTRs.

Samenvatting

In dit proefschrift zijn klinische studies over genitale psoriasis en over HPV-gerelateerde (pre)maligniteiten bij vrouwelijke niertransplantatiepatiënten beschreven.
De twee hoofdthema's van dit proefschrift worden geïntroduceerd in ***Hoofdstuk 1***. Er wordt in dit hoofdstuk een overzicht gegeven van de huidige kennis over epidemiologie, klinische presentatie, diagnose en behandeling van genitale psoriasis. Daarnaast geeft *Hoofdstuk 1* een introductie op de onderwerpen niertransplantatie, immuunsuppressieve therapie en genitale (pre)maligniteiten die ontstaan na transplantatie. *Hoofdstuk 1* eindigt met een beschrijving van therapeutische concessies die vaak gedaan moeten worden bij vrouwelijke niertransplantatiepatiënten met genitale (pre) maligniteiten en mogelijkheden tot preventie.

Deel A: Genitale psoriasis

In ***Hoofdstuk 2*** worden de prevalentie en andere epidemiologische kenmerken van genitale psoriasis in Nederland beschreven. Door middel van vragenlijstonderzoek is vastgesteld dat tot 46% van de psoriasispatiënten genitale psoriasislaesies heeft gedurende het beloop van hun huidziekte. Genitale psoriasis kan zich op elke leeftijd manifesteren. *Hoofdstuk 2* toont tevens aan dat 38% van de patiënten met genitale psoriasis geen betrokkenheid van de huidplooien heeft. Hieruit wordt geconcludeerd dat minimaal een derde van de psoriasispatiënten ook genitale laesies heeft die niet geassocieerd zijn met flexurale psoriasis. Er wordt gesteld dat flexurale en genitale psoriasis zeer waarschijnlijk aparte manifestaties van psoriasis zijn en ook apart aandacht behoeven. *Hoofdstuk 2* pleit voor meer aandacht voor de genitale regio van zowel mannen als vrouwen met psoriasis, ongeacht hun leeftijd.

De kwaliteit van leven en (aandacht voor) seksuele gezondheid van patiënten met genitale psoriasis worden bestudeerd in ***Hoofdstuk 3***. Dit hoofdstuk illustreert dat patiënten met genitale psoriasis een significant slechtere kwaliteit van leven hebben dan psoriasispatiënten zonder genitale laesies. Ook de seksuele gezondheid is verminderd bij een aanzienlijk aantal psoriasispatiënten, met name bij vrouwen met genitale psoriasis. Dit hoofdstuk onderstreept het belang van aandacht voor de impact van (genitale) psoriasis op psychosociale en seksuele gezondheid.

De rol van artsen bij de zorg voor patiënten met genitale psoriasis wordt onderzocht in ***Hoofdstuk 4***. Tevens worden de symptomen van genitale psoriasis, zoals deze door patiënten worden ervaren, bestudeerd. Uit deze studie blijkt dat de overgrote meerderheid van patiënten met genitale psoriasis matige tot ernstige klachten ervaart, waarbij de helft van deze patiënten dit niet bespreekt met hun behandelaar. Tevens laat *Hoofdstuk 4* zien dat meer dan tweederde van de patiënten met genitale

psoriasis nooit behandeld wordt voor hun genitale laesies. Concluderend beschrijft dit hoofdstuk dat de consultatiegraad voor genitale psoriasislaesies laag is, terwijl veel patiënten een aanzienlijke ziektelast ervaren. Om patiënten met genitale psoriasis adequaat te identificeren en te behandelen, wordt een actieve benadering, waarbij de patiënt centraal staat, aanbevolen.

De waarde van gespecialiseerde zorg voor patiënten met genitale psoriasis wordt bekeken in ***Hoofdstuk 5***. Patiënten met genitale psoriasis werden hiertoe uitgenodigd gedurende minimaal een jaar behandeld en ondersteund te worden op een gespecialiseerde polikliniek. Hier werd uitgebreide aandacht aan genitale psoriasis en de impact op (psychoseksuele) kwaliteit van leven gegeven. Zowel de ernst van genitale psoriasis als de kwaliteit van leven van patiënten vertoonde significante verbetering binnen de eerste follow-up periode van ongeveer 6 weken. Bij vrouwen verbeterde ook de seksuele gezondheid significant. Op basis van de bevindingen in dit hoofdstuk wordt geconcludeerd dat genitale psoriasis relatief eenvoudig behandeld kan worden binnen een beperkte tijdsspanne waarbij ook de kwaliteit van leven van patiënten significant verbetert. Routinematige aandacht voor mogelijk aanwezige genitale psoriasis en de daarbij behorende impact op (psychoseksuele) kwaliteit van leven wordt aanbevolen.

Deel B: HPV-gerelateerde genitale (pre)maligniteiten bij vrouwelijke niertransplantatiepatiënten

Het is bekend dat immuunsuppressieve therapie bij niertransplantatiepatiënten geassocieerd is met een verhoogd risico op het ontwikkelen van genitale (pre) maligniteiten. Derhalve wordt bij vrouwelijke niertransplantatiepatiënten frequentere genitale screening geadviseerd, hoewel er geen bewijs is dat dit daadwerkelijk de morbiditeit en mortaliteit als gevolg van genitale (pre)maligniteiten verlaagt. In ***Hoofdstuk 6*** wordt beschreven dat in een cohort van 224 vrouwelijke niertransplantatiepatiënten geen jaarlijkse cervixscreening plaatsvindt. Tevens is het verhoogde risico van de vrouwelijke niertransplantatiepatiënten in dit cohort op de ontwikkeling van genitale (pre)maligniteiten bepaald: 2 tot 6-voudig voor cervicale intraepitheliale neoplasie, 3-voudig voor cervixcarcinoom en 50-voudig voor vulvacarcinoom. Dit hoofdstuk benadrukt het belang van voldoende aandacht voor cervixscreening en inspectie van de anogenitale huid bij vrouwelijke niertransplantatiepatiënten.

Hoofdstuk 7 geeft een overzicht van alle na transplantatie optredende anogenitale (pre)maligniteiten die zich bij vrouwelijke niertransplantatiepatiënten gedurende 40 jaar niertransplantatie in ons centrum ontwikkelden. Tevens wordt de genotype-specifieke prevalentie van HPV in deze (pre)maligniteiten geanalyseerd. *Hoofdstuk 7* toont dat anogenitale maligniteiten bij vrouwelijke niertransplantatiepatiënten vaak

voorkomen en dat deze vrijwel allemaal HPV-gerelateerd zijn. Het is opmerkelijk dat in geval van multifocale laesies bij een patiënt regelmatig verschillende hoog-risico HPV-genotypen aanwezig zijn op de verschillende locaties. Dit duidt erop dat immuungecompromitteerde niertransplantatiepatiënten vatbaar zijn voor herhaaldelijke en onafhankelijke infecties met verschillende HPV-genotypen. In *Hoofdstuk 7* wordt de nadruk gelegd op het belang van anogenitale screening en controle voorafgaand aan en periodiek na niertransplantatie.

Wetende dat immuunsuppressieve therapie geassocieerd is met een toename van HPV-gerelateerde anogenitale (pre)maligniteiten, wordt in ***Hoofdstuk 8*** de genotype-specifieke prevalentie van HPV-infecties in een groot cohort vrouwelijke niertransplantatiepatiënten getoetst. Uit analyse van cervicovaginale samples die verkregen zijn middels een zelftest blijkt dat de punt-prevalentie van mucosaal HPV bij vrouwelijke niertransplantatiepatiënten 27.1% in het algemeen en 17.4% voor hoog-risico HPV in het bijzonder is. Dit is evident hoger dan in de algemene populatie. *Hoofdstuk 8* laat tevens zien dat bij vrouwelijke niertransplantatiepatiënten de HPV-genotypes verschuiven in vergelijking met de algemene populatie. Middels anogenitale screening van alle HPV-positieve patiënten identificeert deze studie een belangrijk aantal vrouwelijke niertransplantatiepatiënten met verborgen genitale premaligniteiten. Het introduceren van zelftests op HPV-infecties kan behulpzaam zijn bij het tijdig ontdekken van (pre) maligne anogenitale laesies bij niertransplantatiepatiënten.

CHAPTER

11

Dankwoord

Bibliography

Curriculum Vitae

Dankwoord

Zomer 2014, Wyler

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Curriculum Vitae

Kim Meeuwis werd op 17 april 1983 geboren in Berkel-Enschot. Daar groeide ze op en ging er naar de basisschool. Tijdens haar schooljaren was Kim actief in de paardensport en speelde zij in een blokfluitkwartet. In 2001 behaalde zij haar vwo-diploma aan het Theresialyceum in Tilburg. Nadat zij aanvankelijk was uitgeloot voor de studie Geneeskunde, behaalde zij in 2002 haar propedeuse Medische Biologie aan de Radboud Universiteit Nijmegen. In datzelfde jaar mocht zij starten met de studie Geneeskunde aan deze faculteit. Kim ontwikkelde al tijdens haar studie een grote interesse in de specialismen Dermatologie en Gynaecologie. Daarom koos zij ervoor om een seniorcoschap Dermatologie en een keuzecoschap Verloskunde & Gynaecologie te volgen. Haar wetenschappelijke stage verrichtte zij op de afdelingen Dermatologie en Verloskunde & Gynaecologie van het UMC St Radboud onder leiding van dr. M.M. van Rossum en dr. J.A. de Hullu. Tijdens deze stage hield zij zich bezig met HPV-gerelateerde anogenitale problematiek bij niertransplantatiepatiënten. Nadat ze haar doctoraalexamen in november 2008 behaalde, werd Kim aangesteld als promovendus om deze onderzoekslijn voort te zetten. Daarnaast zette zij een onderzoekslijn naar genitale psoriasis op. Ze werd hierbij begeleid door prof. dr. P.C.M. van de Kerkhof, prof. dr. L.F.A.G. Massuger, dr. M.M. van Rossum en dr. J.A. de Hullu. Tijdens de najaarsronde van 2010 werd een AGIKO-stipendium intern gehonoreerd, waardoor de onderzoeksprojecten die hebben geleid tot dit proefschrift konden worden voortgezet en uitgebreid. In 2012 startte Kim naast haar onderzoek als arts op de vulvapoli van het UMC St Radboud, waar zij met veel enthousiasme de zorg voor patiënten met vulvaire klachten had. Daarnaast is zij sinds 2012 bestuurslid van de Nederlandse Vereniging voor Vulvapathologie. Kim is sinds juli 2013 in opleiding tot dermatoloog aan het Radboudumc te Nijmegen. Ze woont samen met Sjoerd Neijenhuis en hun twee Afrikaanse jachthonden Hedaya en Dalewa in het Duitse Wyler.