Oral Mucosal Lesions and Oral Health-Related Quality of Life in Persons Attending a Dermatology Clinic in Khartoum, Sudan

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The seeking of knowledge is obligatory for every Muslim, both male and female.

Prophet Muhammad[pbuh]
Scientific environment

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Nada Mohamed Suliman

24 June, 2013
List of abbreviations

ABSIS  Autoimmune bullous skin disorder intensity score
AIDS  Acquired immunodeficiency syndrome
CI  Confidence interval
COMDQ  Chronic oral mucosal diseases quality of life questionnaire
DIF  Direct immunofluorescence
DMFT  Decayed, missing and filled teeth, due to caries in permanent dentition
Dsg  Desmogleins
ELISA  Enzyme-linked immunosorbent assay
HIV  Human immunodeficiency virus
HLA  Human leukocyte antigen
ICIDH  International classification of impairment, disabilities and handicaps
IIF  Indirect immunofluorescence
IgG  Immunoglobulin G
IHC  Immunohistochemistry
KTH  Khartoum Teaching Hospital
OHIP  Oral health impact profile
OHRQoL  Oral health-related quality of life
OIDP  Oral impact on daily performance
OLAS  Oral Lesion Activity Score
OML  Oral mucosal lesions
OSCC  Oral squamous cell carcinomas
OR  Odds ratio
PDAI  Pemphigus disease area index
PF  Pemphigus foliaceus
PV  Pemphigus vulgaris
QoL  Quality of life
RAU  Recurrent aphthous ulcers
SCC  Squamous cell carcinomas
SMoH  State Ministries of Health
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>SPSS</td>
<td>Statistical package for social sciences</td>
</tr>
<tr>
<td>UST</td>
<td>University of Science and Technology</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Abstract

Background: The mucous membrane of the oral cavity is the site of many neoplasms, reactive processes, infections and manifestation of systemic diseases. Lesions in the oral mucosa may be the primary clinical feature or the only sign of muco-cutaneous diseases. Some conditions can result in considerable morbidity and mortality if not properly treated. Patients with such conditions may often consult a dermatology clinic. Information on the diversity, magnitude and burden of these conditions in general is rare in Africa and specifically in Sudan. To plan for effective oral health services, correct diagnosis based on proper investigations and epidemiological studies are essential.

Objective: This study aimed to explore the diversity of pathological and non-pathological conditions of the oral mucous membrane in patients with skin lesions attending the outpatient facility of Khartoum Teaching Hospital (KTH) - Dermatology Clinic, Sudan. The study also had the following specific objectives: to estimate the frequency and socio-behavioural distribution of oral mucosal lesions (OML) in patients with skin diseases; to assess the impact of these conditions on patients’ daily life activities using the Arabic version of the Oral Impact on Daily Performances (OIDP) inventory in patients with and without OML; and, to describe clinical features of oral pemphigus in persons attending the outpatient clinic.

Methods: From October 2008 to January 2009, all outpatients aged above 18 years attending the dermatology clinic of KTH were invited to participate in a cross-sectional hospital-based study. Data were collected by face-to-face interviews using structured questionnaires followed by clinical examinations of the skin and the oral cavity. Oral cavity clinical examinations, diagnosis of OML and decayed, missing and filled teeth (DMFT) registration were performed following the World Health Organization (WHO) criteria. Biopsies, smears and immunohistochemistry (IHC) were used as adjuvant techniques for confirmation. An Arabic version of the OIDP inventory was used to assess oral health related quality of life.
**Results:** In Paper 1, OML were registered in 315 out of 544 (57.9%) patients with confirmed skin diseases. *Tongue lesions* were the most frequently diagnosed OML (23.3%), followed in descending order by *white lesions* (19.1%), *red and blue lesions* (11%) and *vesiculobullous diseases* (6%). Presence of OML in patients with skin disease was most common in older age groups (p<0.05), in males (p<0.05), patients who reported systemic disease (p<0.05) and among current users of smokeless tobacco (toombak) (p<0.00).

In Paper II, at least one oral impact (OIDP > 0) was reported by 190 patients (35.6%). The prevalence of any oral impact was 30.5%, 36.7% and 44.1 % in patients with no OML, one type of OML and more than one type of OML, respectively. The number of types of OML and the number and types of oral symptoms were consistently associated with the OIDP scores. Patients who reported bad oral health, ≥ 1 dental attendance, > 1 type of OML, or ≥ 1 type of oral symptom were more likely than their counterparts in the opposite groups to report any OIDP. The odds ratios (OR) were respectively; 2.9 (95% CI 1.9-4.5), 2.3 (95% CI 1.5-3.5), 1.8 (95% CI 1.1-3.2) and 6.7 (95% CI 2.6-17.5). Vesiculobullous and ulcerative lesions of OML disease groups were statistically significantly associated with OIDP.

In Paper III, nineteen of 21 patients with PV had oral lesions (mean age 43.0, range 20 – 72 yrs.). Of 18 patients who had experienced both skin and oral lesion during their lifetime, 50% reported that oral lesions preceded skin lesions. More than 68% (13/19) of these patients were < 50 years of age, with female: male ratio of 1.1:1. The palatal and buccal mucosae were the most common locations followed by tongue and lower lip. The Oral Lesion Activity Score (OLAS) was higher in those who reported living outside of Khartoum, were outdoor workers, had lower education and belonged to central and Western tribes, compared with their counterparts. The histopathological pictures of all specimens were in agreement with the IHC findings.

**Conclusions:** OML were frequently diagnosed in patients with skin disease and varied with age, gender, systemic condition and use of toombak. OIDP occurred more frequently among patients with skin disease with OML, compared with patients with
skin disease without OML. The Arabic version of the OIDP inventory used in this study showed acceptable and reliable psychometric properties. The majority of PV patients had oral lesions. The socio-demographic, clinical and histological pictures of oral PV are in accordance with the literature. The IHC on formalin-fixed tissue samples may be an alternative test to confirm the diagnosis of PV. The results of this study shed light on the higher prevalence of OML in patients with dermatologic diseases and thus emphasize the importance of routine examination of the oral mucosa in these patients. Collaboration efforts between dermatologists and dentists would provide better treatment and avoid serious morbidity and mortality.
List of publications

This thesis is based on the following original papers:

**Paper I**


**Paper II**


**Paper III**

**Suliman NM, Åstrøm AN, Ali RW, Salman H, Johannessen AC:** *Clinical and histological characterization of oral pemphigus lesions in dermatologic patients: a cross sectional study from Sudan.* (In manuscript)
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1. Introduction

1.1 Oral mucosal lesions - definitions and public health aspects

The term *mucous membrane* is defined as the moist lining of the oral cavity, gastrointestinal tract, nasal passages, and other body cavities that connect with the exterior. In the oral cavity, this lining is called the oral mucous membrane or oral mucosa. At the lips, the oral mucosa is continuous with the skin and in the pharynx it is continuous with the moist mucosa lining the rest of the gut [1]. Oral mucosal lesions (OML) in the present thesis have been defined as any abnormal change or any swelling in the oral mucosal surface. It is known that the oral cavity, including the oral mucosa, is the host of neoplasms, reactive processes, infections, and manifestations of many systemic body physiological and pathological changes [2, 3]. In this respect, the oral mucosa mirrors the patient’s general health [4]. It is noteworthy that oral health workers face a tremendous variety of lesions ranging from uncommon to common conditions and traversing from life-threatening diseases to the most innocent and hereditary ones. More than 200 mucosal conditions have been documented [5]. Andreasen et al. [6] reviewed the epidemiology of some common oral disorders, other than dental caries and periodontal disease, which affect the oral and maxillofacial structures. The review revealed that 25% to 50% of the populations examined had oral mucosal diseases, which comprised a tremendous variety of lesions including malignant ones. In 2003, the World Health Organization (WHO) described OML as one of the major public health problems worldwide [7, 8].

Globally, OML have been studied from different points of view; clinical aspects, histology, pathogenesis, etiology, and treatment modalities. Only a few epidemiological studies have focused on OML at the global level [8]. From a public health point of view, Pindborg stated: “The diseases with the highest priority would be those which are the most dangerous, and those which are the most prevalent
provided the latter present a therapeutic problem. Also of interest would be such oral mucosal diseases, which, although rare, are of great nuisance to the patients. In this connection, it should be emphasized that numerous OML are expressions, often the first, of systemic diseases”[9]. In that connection, the 1960s and 1970s witnessed interest of the WHO in OML and listed the most prime diseases of interest to be; oral carcinoma, leukoplakia, erythroplakia, leukokeratosis nicotina palati, lichen planus, submucous fibrosis, herpetic gingivostomatitis, acute necrotizing gingivitis, cancru oris, candidiasis, and aphthous ulcerations [9].

Another public health threat, the acquired immunodeficiency syndrome (AIDS), has been recognized as the leading cause of death in Sub-Saharan Africa and the fourth-leading cause of mortality world-wide [10]. Between 60% and 90% of the people with human immunodeficiency virus (HIV) infection will have at least one oral lesion at a period of time during the development of the disease [11]. Pseudomembranous candidiasis, hairy leukoplakia, Kaposi sarcoma, periodontal diseases and non-Hodgkin’s lymphoma are considered to have strong associations with HIV/AIDS. Moreover, hyperpigmentation, necrotizing stomatitis, salivary gland diseases, and bacterial and viral infections have moderate associations with the disease. Since the onset of the HIV pandemic, oral lesions have been well recognized as early indicators of HIV infection and as predictors of HIV disease progression [11].

Although some diseases only affect the oral cavity in many occasions, the mouth is a mirror of associated skin diseases or underlying systemic conditions [4]. The epithelium of the oral cavity and skin originates from the same embryonic ectoderm, while the posterior third of the tongue originates from endoderm. Thus, the skin and oral mucosa share some properties, and diseases may manifest themselves both in oral mucosa and skin [1, 3, 12]. The most important skin diseases with oral manifestations are listed in Table 1. These diseases have been described in a number of review papers [13-17]. Of particular concern in this study is oral pemphigus vulgaris.
Table 1: Skin Diseases With Oral Manifestations [18]

<table>
<thead>
<tr>
<th>Genetic-related diseases</th>
<th>Oral manifestation</th>
<th>Immune-related diseases</th>
<th>Oral manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectodermal dysplasia</td>
<td>Xerostomia, hypodontia, anodontia, dental deformity</td>
<td>Pemphigus</td>
<td>Bullae, erosion, ulcers</td>
</tr>
<tr>
<td>White sponge nevus</td>
<td>Thick white, corrugated or velvety, diffuse plaques affect the buccal mucosa, bilaterally in most instances</td>
<td>Paraneoplastic pemphigus</td>
<td>Bullae, erosion, ulcers, hemorrhagic crusted lips</td>
</tr>
<tr>
<td>Hereditary benign intraepithelial dyskeratosis</td>
<td>Thick white corrugated plaques (buccal and labial mucosa in most instances)</td>
<td>Mucous membrane pemphigoid</td>
<td>Bullae, erosion, ulcers</td>
</tr>
<tr>
<td>Pachyonychia congenita</td>
<td>Thick white plaques (lateral margins and dorsal surface of the tongue)</td>
<td>Linear IgA dermatosis</td>
<td>Bullae, erosion, ulcers</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>Bullae followed by erosion and eventually hyperkeratosis (tongue, buccal mucosa), progressive periodontal diseases. Leukoplakic lesions considered premalignant lesions</td>
<td>Angina bullosa hemorrhagica</td>
<td>Blood-filled vesicles or bullae</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>OSCC of the lower lip and the tip of the tongue</td>
<td>Epidermolysis bullosa acquisita</td>
<td>Bullae, erosion, ulcers, constricted oral orifice, hypoplastic teeth</td>
</tr>
<tr>
<td>Hereditary mucoepithelial dysplasia</td>
<td>Asymptomatic demarcating fiery-red erythema of the hard palate Less involvement (attached gingivae, tongue mucosa)</td>
<td>Bullous pemphigoid</td>
<td>Bullae, erosion, ulcers</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>Hypodontia (oligodontia), dental hypoplasia, delayed eruption</td>
<td>Erythema multiforme</td>
<td>Erosion, ulcers, hemorrhagic crusted lips</td>
</tr>
<tr>
<td>Darier’s disease</td>
<td>Multiple, normal-coloured or white, flat-topped papules (Hard palate, alveolar mucosa)</td>
<td>Reactive arthritis (Reiter’s syndrome)</td>
<td>Erythematous papules, shallow ulcers, geographic tongue</td>
</tr>
<tr>
<td>Warty dyskeratoma</td>
<td>Pink or white umbilicated papule (keratinized)</td>
<td>Lichen planus</td>
<td>Interlacing white lines bilaterally on the posterior</td>
</tr>
<tr>
<td>Condition</td>
<td>Clinical Features</td>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td></td>
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<tr>
<td>(isolated Darier’s disease)</td>
<td>mucosa</td>
<td>buccal mucosa (Wickham’s striae),</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>atrophic erythematous area with</td>
<td></td>
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<td></td>
<td></td>
<td>central ulceration, white plaques</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>replacing normal papillary surface</td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Brown to blue-gray macules freckle-like lesion (primary vermilion zone)</td>
<td>Graft-versus-host disease</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Resemble oral lichen planus, pinpoint</td>
<td></td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>Red papules blanched on diascopy</td>
<td>Psoriasis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>White plaque, red plaque, ulcers,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>erythema migrans (not confirmed)</td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos syndromes</td>
<td>Marked elasticity of the tongue (an ability to touch tip of the nose with the</td>
<td>Lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tongue (Gorlin’s sign)), friability of oral mucosa, hypermobility of TMJ, dental</td>
<td>Ulcers, erythema, hyperkeratosis,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>abnormality</td>
<td>xerostomia</td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Enamel pitting on the facial aspect of the anterior permanent dentition.</td>
<td>Systemic sclerosis</td>
<td></td>
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<td></td>
<td>Multiple fibrous papules, diffuse fibrous gingival enlargement (angiofibroma)</td>
<td>Microstomia, loss of attached</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>gingival mucosa, gingival</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>recession, xerostomia</td>
<td></td>
</tr>
<tr>
<td>Multiple hamartoma syndrome</td>
<td>Multiple papules affecting gingivae, dorsum of tongue and buccal mucosa. High</td>
<td>CREST syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>arched palate, periodontitis, extensive dental caries</td>
<td>Telangiectasias</td>
<td></td>
</tr>
<tr>
<td>Epidermolysis bullosa</td>
<td>Ulcers, microstomia, ankyloglossia, dental deformity, severe caries.</td>
<td>Acanthosis nigricans</td>
<td></td>
</tr>
<tr>
<td>Palmoplantar keratoderma</td>
<td>White lesions (leukokeratosis)</td>
<td>Fine papillary area of mucosal</td>
<td></td>
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<td></td>
<td></td>
<td>alteration</td>
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</table>
1.2 Prevalence of OML globally

Epidemiological investigations of OML may be grouped into three categories: studies on oral cancer, studies on specific lesions other than cancer, such as recurrent aphthous ulcers (RAU) and recurrent herpes labialis, and studies of the prevalence of OML as a group. Current published studies in the last two categories are few compared with studies of oral cancer, dental caries and periodontal diseases \([8, 19]\).

The prevalence of a disease is the proportion of people in a population that has the disease at a given point in time \([20]\). Population-based studies are the optimal choice to estimate the prevalence of OML but population-based studies are expensive and time consuming \([21]\). A large comprehensive population-based study conducted by Axéll, revealed that 75% of the documented lesions were relatively rare with a prevalence of 0.01-3.8% \([22]\). To investigate rare conditions adequately, most publications considering OML are based on population subgroups like the elderly or school children and on special groups like patients from outpatient clinics and patients with specific diseases \([23-31]\). Focus on the special groups may ensure that patients with rare diseases will be included in the sample.

According to the WHO, oral cancer and precancerous lesions are the most important OML that have been studied \([9]\). Oral cancer is considered the eighth most common cancer worldwide and the third most common cancer in south-central Asia. About 2.6% of all cancers worldwide is oral cancer \([32]\) and oral squamous cell carcinomas (OSCC) constitute more than 90% of these cancers \([33]\). Precancerous lesions such as leukoplakia, erythroplakia and oral submucous fibrosis entail a high risk of malignant transformation, reported to be in the range of 30-80% \([34]\). Thus, identifying these lesions at an early stage is important to initiate proper treatment. The prevalence of oral leukoplakia has been reported to vary from 0.1% among 27,443 adults in Minnesota, USA to 10.6% among 803 individuals aged 15 years and above in Kenya, indicating that leukoplakia varies across geographical locations. Most of the studies on precancerous lesions have been conducted in Southeast Asia \([7, 35, 36]\). National
oral health survey conducted in Sri Lanka, reported a prevalence of erythroplakia between 0.05-0.2% [37]. The prevalence of oral submucous fibrosis, mostly reported from Indian subcontinent, was up to 0.5% [38, 39]. Oral lichen planus as a premalignant lesion showed an annual malignant transformation rate of 0.36% [40]. Among 20,333 Swedish people aged 15 years and above, oral lichen planus was found in 1.9% [41].

Table 2 shows the prevalence of the ten top OML in studies conducted among individuals aged 15 years and above from the general population as well as among dental attendees. In these studies, the types of OML that have been included had great influence on the prevalence reported. For instance, when different types of tongue lesion were taken into account, a higher prevalence of OML was generally reported [22, 27, 42]. The same observation was noted when non-pathologic morphologic alterations such as Fordyce’s granules, geographic and fissured tongue were considered [22, 24, 42]. In these studies, white lesions (frictional lesions, leukoplakia, lichen planus and leukoedema) account for a considerable proportion of OML and were observed in more than 6 studies. Data may also differ if they are collected from case history, rather than from lesions observed at time of examination. This has been shown in RAU and recurrent herpes simplex [22]. Also, several studies have shown that the overall OML prevalence was linked to risk habits, sex and age. Tobacco and use of a denture were significantly linked with the occurrence of leukoplakia, frictional lesions and denture stomatitis [22, 23, 27, 42-45]. An increase in overall OML prevalence was observed with increased age [43, 46]. Nevertheless, these studies have shown that OML such as frictional lesions, leukoplakia, cheek bite, denture stomatitis, lichen planus, fissure tongue, RAU, traumatic lesion, leukoedema, geographic tongue and melanin pigmentation are the ten most observed OML among the studies. The least common OML observed were papilloma and scar.

Table 2 shows that substantial variation exists between the studies in terms of sample size, age, and time allocated for data collection, sampling methods, diagnostic criteria, training and calibration. The absence of consensus among these elements creates
difficulties in comparing results across the various studies [47]. For example, the standardized WHO criteria are valid for most of the OML that were investigated in the studies presented in Table 2, but only 9 out of 17 studies used those criteria. In addition, training and calibration of examiners to achieve accurate diagnosis and a high level of agreement were missing in some studies. Among the studies that reported training and calibration, only a few explained the technique used in details [22, 43] while the majority gave no further information. Using natural or artificial light in a steady manner throughout the data collection would also decrease variation in the prevalence of OML reported. Such information was lacking in the majority of the studies. This means that variation in methodological considerations among OML prevalence studies is a real problem, making comparison among different studies a difficult task [47, 48].

There is a lack of information about the prevalence of OML in Sudan. In 1992, a population-based study conducted in Northern Sudan revealed that the prevalence of snuff dipper’s lesions was 5.1% (281) among 5500 adults over the age of 20 years [49]. Abbas et al. [50, 51] reported two cases of mucosal leishmaniasis with oral manifestations. Visceral, cutaneous and mucosal leishmaniasis are endemic in Sudan, with mucosal leishmaniasis being the least common one.
Table 2: An overview of studies published considering the prevalence of OML between 1976 and 2011 (the ten top OML per each study)

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Sample size (Duration)</th>
<th>Age in years</th>
<th>Population frame Sampling method</th>
<th>Diagnostic criteria</th>
<th>Examiners’ training and calibration, Number (n)</th>
<th>OML %</th>
<th>OML and prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>Sweden</td>
<td>20333</td>
<td>+15</td>
<td>County residents</td>
<td>Axéll</td>
<td>Reported n &gt;1</td>
<td>61.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fordyce’s granules 82.0, leukoedema 48, denture stomatitis 16.0, excessive melanin 9.0, geographic tongue 8.4 , amalgam tattoo 8.2, snuff dipper’s lesion 8.0, fissured tongue 6.4, preleukoplakia 6.3, frictional lesion 5.4</td>
</tr>
<tr>
<td>1986</td>
<td>USA</td>
<td>23616 (16 years)</td>
<td>+35</td>
<td>Oral cancer screening database Retrospective study</td>
<td>Not reported</td>
<td>Reported n &gt;1</td>
<td>21.0</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>number per 1000: leukoplakia 28.9, snuff dipper’s lesion 1.6 , cheek bite 1.2, lichen planus 1.1, smoker’s palate 0.7, leukoedema 0.3</td>
</tr>
<tr>
<td>1988</td>
<td>USA</td>
<td>17.235 (6 years)</td>
<td>+17</td>
<td>NHANES III database Retrospective study</td>
<td>WHO</td>
<td>Reported n &gt;1</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>denture stomatitis 3.6, amalgam tattoo 3.3, cheek bite 3.0, frictional lesion 2.6, nevus 2.0, geographic tongue 1.8, herpes labialis 1.6, scar 1.4, denture hyperplasia 1.1, RAU 0.8</td>
</tr>
<tr>
<td>1995</td>
<td>Cambodia</td>
<td>1319 (27 days)</td>
<td>+15</td>
<td>County residents Invitation</td>
<td>WHO</td>
<td>Reported n =1</td>
<td>4.9</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>lichen planus 1.8, candidiasis 1.4, leukoplakia 1.1, submucous fibrosis 0.2, cancer 0.1, cheek bite 0.2, glossitis unspecified 0.2, angular chelitis 0.5, papilloma 0.1</td>
</tr>
<tr>
<td>1995</td>
<td>Kenya</td>
<td>803 (not reported)</td>
<td>+15</td>
<td>County residents Random sampling</td>
<td>WHO Others</td>
<td>Reported n =1</td>
<td>48.6</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>leukoedema 26.0, melanin pigmentation 12.7, leukoplakia 10.6, palatal keratosis 6.4, frictional lesion 5.5, preleukoplakia 4.1, borderline leukoplakia 2.4, cheek and lip bite 1.3, snuff dipper’s lesion 0.4</td>
</tr>
<tr>
<td>1997</td>
<td>Malaysia</td>
<td>11697 (5 months)</td>
<td>+25</td>
<td>County residents Random sampling</td>
<td>WHO Axéll Others</td>
<td>Reported n &gt;1</td>
<td>9.7</td>
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<td></td>
<td></td>
<td>number per 1000; denture stomatitis 33.5, other lesions 25.8, betel chewer’s mucosa 16.0, leukoplakia 9.6, smoker’s palate 4.9, angular chelitis 3.9, lichen planus</td>
</tr>
<tr>
<td>Year</td>
<td>Country</td>
<td>Sample Size</td>
<td>Age</td>
<td>Setting</td>
<td>Method</td>
<td>Number</td>
<td>Lesions</td>
<td></td>
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<tr>
<td>[42]</td>
<td>Slovenia</td>
<td>555</td>
<td>15, 35, 45, 55, 65</td>
<td>County residents Random sampling</td>
<td>WHO Axell Others</td>
<td>Not reported n =1</td>
<td>61.6 Fordyce’s granules 49.7, fissured tongue 21.1, varices 16.2, denture stomatitis 4.3, leukoplakia 3.1, cheek bite 2.7, lichen planus 2.3, frictional lesion 2.2, geographic and fissured tongue 1.1, mucocele 0.9</td>
<td></td>
</tr>
<tr>
<td>[23]</td>
<td>Spain</td>
<td>337</td>
<td>≥30</td>
<td>Dental clinic attendees Census</td>
<td>WHO Others</td>
<td>Not reported n &gt;1</td>
<td>58.7 melanin pigmentation 24.6, frictional lesion 11.5, linea alba 10.1, cheek biting 6.8, fissured tongue 5.0, traumatic lesion 4.7, hemangioma 3.2, denture stomatitis 2.6, herpes labialis 2.3, RAU 2.3</td>
<td></td>
</tr>
<tr>
<td>[27]</td>
<td>Spain</td>
<td>308</td>
<td>+30</td>
<td>County residents Random sampling</td>
<td>WHO Others</td>
<td>Not reported n &gt;1</td>
<td>51.1 varices 21.0, frictional lesion 7.5, traumatic lesion 7.1, denture stomatitis 6.5, excessive melanin 5.8, denture hyperplasia 5.2, fissured tongue 3.9, lichen planus 3.2, cheek bite 2.9, angular chelitis 2.9, coated tongue 2.9</td>
<td></td>
</tr>
<tr>
<td>[46]</td>
<td>Germany</td>
<td>4210</td>
<td>≥21</td>
<td>County residents Random sampling</td>
<td>Not reported</td>
<td>Not reported n &gt;1</td>
<td>11.83 leukoplakia simplex 2.8, leukoplakia verrucosa 0.05, leukoplakia erosive 0.02, erythroplakia 0.02, lichen planus 0.4, ulcer 0.7, exophytic neoplasia 3.0, herpetiform/aphthous ulcers 1.6, other lesions 2.9</td>
<td></td>
</tr>
<tr>
<td>[55]</td>
<td>Mexico</td>
<td>23785</td>
<td>+15</td>
<td>Dental attendees data base Retrospective study</td>
<td>Others</td>
<td>Not reported n &gt;1</td>
<td>Number per 1000; leukoedema 105.3, traumatic lesion 40.2, frictional lesion 32.1, traumatic erythema 28.5, morsicatio buccarium (cheek bite) 21.6, chronic atrophic candidiasis (denture stomatitis) 20.1, inflammatory fibrous hyperplasia (denture hyperplasia) 15.8, RAU 8.5, herpes labialis 7.9, geographic tongue 7.6</td>
<td></td>
</tr>
<tr>
<td>[43]</td>
<td>Italy</td>
<td>4098</td>
<td>≥19</td>
<td>Cancer screening data base Retrospective study</td>
<td>WHO Axell</td>
<td>Reported n &gt;1</td>
<td>25.0 traumatic lesion 2.9, cheek bite 2.2, denture stomatitis 1.9, fibroma/fibrous hyperplasia 1.7, vascular lesions 1.7, frictional lesion 1.7, RAU 1.7, lichen planus 1.4, candidiasis 1.4, leukoplakia 1.1</td>
<td></td>
</tr>
<tr>
<td>[25]</td>
<td>Saudi Arabia</td>
<td>2552</td>
<td>+15</td>
<td>Dental clinic attendees Census</td>
<td>Not reported</td>
<td>Not reported n =1</td>
<td>15.0 Fordyce’s granules 3.8, leukoedema 3.3, traumatic lesion 1.8, fissured tongue 1.4, torus platinus 1.3, frictional lesion 0.9, tongue tie 0.5, melanin pigmentation 0.5, hairy tongue 0.5, geographic tongue</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Location</td>
<td>Sample Size</td>
<td>Age</td>
<td>Setting</td>
<td>Census Method</td>
<td>Other Lesions</td>
<td>RAU</td>
</tr>
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<td>-----------</td>
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</tr>
<tr>
<td>[24] 2009 Iran</td>
<td>598 (a year)</td>
<td>≥19</td>
<td>Dental clinic attendees</td>
<td>Not reported</td>
<td>Not reported</td>
<td>49.3</td>
<td>Fordyce’s granules 27.9, fissured tongue 12.9, leukoedema 12.5, hairy tongue 8.9</td>
<td></td>
</tr>
<tr>
<td>[56] 2009 Turkey</td>
<td>5000 (16 month)</td>
<td>≥17</td>
<td>Dental clinic attendees</td>
<td>WHO</td>
<td>Reported</td>
<td>15.5</td>
<td>Absolute numbers: RAU 116, coated tongue 107, secondary herpes (herpes labialis) 102, fissured tongue 48, traumatic lesion 46, morsicatio buccarium (cheek bite) 36, frictional lesion 29, fibro-epithelial hyperplasia 29, tongue atrophic papillae 25, melanin pigmentation 24</td>
<td></td>
</tr>
<tr>
<td>[57] 2009 USA</td>
<td>3.182 (3 weeks)</td>
<td>adult</td>
<td>Dental clinics attendees</td>
<td>Others</td>
<td>Reported</td>
<td>26.7</td>
<td>frictional lesion 7.6, amalgam tattoo 3.7, traumatic lesion 3.4, fissured tongue 2.5, fibroma/fibrous hyperplasia 2.4, smoker's palate 1.3, geographic tongue 1.2, burns 1.0, snuff dippers lesion 0.8, leukoplakia 0.7</td>
<td></td>
</tr>
<tr>
<td>[45] 2011 Sangli, India</td>
<td>24.422 (18 months)</td>
<td>Not reported</td>
<td>Dental clinic attendees</td>
<td>Not reported</td>
<td>Not reported</td>
<td>2.5</td>
<td>RAU 0.7, submucous fibrosis 0.6, cancer 0.3, leukoplakia 0.3, lichen planus 0.1, fibroma/fibrous hyperplasia 0.1, denture stomatitis 0.09, pyogenic granuloma 0.07, submucous fibrosis + leukoplakia 0.05</td>
<td></td>
</tr>
</tbody>
</table>
1.3 Biological, socio-demographic and behavioural factors associated with OML

Risk has been defined as “a probability of an adverse outcome, or a factor that raises this probability” [58]. By definition, a risk factor must clearly establish that the exposure has occurred before the outcome [59]. Thus, longitudinal studies are essential to launch risk factors, whereas cross-sectional studies can only provide evidence of risk indicators.

The oral cavity of healthy individuals harbors hundreds of bacterial, viral, and fungal species, many of which are commensal ones. Pathogenic ones, which could constitute biological risk factor for OML, colonize and overgrow in response to changes in the host immunity, micro-environment or other triggers in the oral cavity such as food or dental material. In addition to the above mentioned biological risk factors, OML are strongly related to behavioral and socio-economic status. Thus, the OML are multifactorial diseases which may have a number of various risk factors rather than a single cause. Table 3 lists some of the factors affecting the oral mucosal tissues. Generally, lifestyle related factors have a great influence on oral diseases [8]. Evidently, tobacco either in smoke- or smokeless form constitutes an important risk factor for many oral diseases, including OML [60, 61]. Studies have demonstrated a dose-response relationship between tobacco usage and OML. These diseases can be listed as; smoker’s palate (stomatitis nicotina) [62], smoker’s melanosis [43], palatal keratosis (associated with reverse smoking), frictional keratosis [43], coated /hairy tongue [63], oral candidiasis, median rhomboid glossitis [64], snuff-dipper’s lesion [65], leukoplakia [66], erythroplakia [67] and OSCC. A number of review papers have described these diseases in general [61, 68-71]. Tobacco use in various forms has been estimated to account for over 90% of cancers in the oral cavity, with increased risks when tobacco use is combined with alcohol [72, 73]. In South and South-East Asia, 90% of oral cancer are attributed to tobacco use combined with areca nut/betel quid chewing, heavy alcohol drinking and dietary micronutrient deficiency[74]. In Sudan,
the role of toombak (smokeless tobacco) has been stated to be of major importance in the aetiology of oral squamous cell carcinoma [75]. Idris et al. [75] studied 1,916 cases of oral neoplasms registered in Sudan Cancer Registry from 1970 to 1985, and found that 66.5% of oral malignancy was OSCC, followed by tumors of the salivary gland, neoplasms of non-odontogenic and non-epithelial origin and odontogenic neoplasm. Men had a higher frequency than women, and the lesions were more prevalent in older age. The betel quid chewing was found to be a significant etiological factor of submucous fibrosis in a case-control study in Sri Lanka [76].

With connection to lifestyle related factors, about 21% of Waimiri-Atroani Indians in Brazil, showed focal epithelial hyperplasia, an infectious condition that have been connected with close living conditions, dietary insufficiency and poverty in many ethnic and racial groups [77, 78]. The role of denture use as a risk factor for stomatitis has been extensively studied and reviewed, reporting prevalence of denture stomatitis ranging from 17% to 71% among denture wearers [79-84].

A cross sectional study from India conducted among 1187 employees of Mysore city found that the prevalence of oral pre-malignant and malignant lesions was higher in individuals with lower compared to individuals with higher socio-economic status [85]. Similar results have been obtained by a case-control study using data from the baseline screening of a randomized oral cancer screening trial in Kerala, India [86]. In a study of 202 agricultural workers in Brazil, the prevalence of actinic cheilitis was 39.6%, where formal education and more than four years education were found to decrease the risk for actinic cheilitis [87]. A total of 362 beach workers from Brazil exhibited 15.5% of actinic cheilitis. The study found that beach workers with lower education (up to 6 years of schooling) were 1.7 times more likely to have actinic cheilitis than those with more than 6 years of education [88].

A number of studies have revealed that outdoor workers who are exposed to higher solar radiation time have a higher probability of developing actinic cheilitis. The prevalence of actinic cheilitis have been reported to vary between 15% and 43% among outdoor workers [87-89], while in the general population the prevalence has
varied between 0.4 and 2.4% [88]. Another study from Brazil revealed 16.7% of actinic cheilitis among 240 farmers [89].

Some investigators have reported that the prevalence of OML increases with increasing age, and being a male. In a study done on 598 referred Iranian patients, the prevalence of patients with OML increased significantly with age from 25.8% in the youngest age group (<19 years) to 74.3% in the oldest group (≥ 60 years). The study also found that OML occurred more frequently in men (62.4%) than in women (37.6%) (P<0.004) [24]. Similar results were found in the NHANES III data, showing that individuals aged ≥ 70 years almost twice the odds of having OML as compared with the youngest age group (17 - 29 years). The same study showed that males had significantly larger odds of having OML than females [44]. In general, older people are more susceptible for systemic diseases and have been exposed to risk factors throughout their life course, such as for instance tobacco, alcohol and multiple medications. Besides, males and females often have differing degrees of exposure to some of the lifestyle and environmental risk factors. One of the main significant risk factors for OML associated with autoimmune dysfunction is ethnicity and being females [90]. Genetic factors are suggested to play a role in ethnic disparities [91]. Other risk factors for OML include physical trauma, physical chronic irritation and chemical irritation.

In conclusion, the risk factors responsible for OML are numerous, and previous studies have put more emphasis on behavioral risk factors rather than socio-economic factors in relation to OML. Control of OML depends on the availability and accessibility of the oral health systems, but risk reduction is only possible if services are focused on primary health care and prevention.
Table 3: Factors affecting oral mucosal lesions. Table adapted from Kleinman et al. [19]

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Hygiene</td>
</tr>
<tr>
<td>Environmental</td>
<td>Ultraviolet radiation</td>
</tr>
<tr>
<td></td>
<td>Occupation</td>
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<tr>
<td>Infectious Agents</td>
<td>Bacterial</td>
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<tr>
<td></td>
<td>Viruses</td>
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<td></td>
<td>Parasites</td>
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<tr>
<td></td>
<td>Fungal</td>
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<tr>
<td>Host Factors</td>
<td>Genetic predisposition</td>
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<tr>
<td></td>
<td>Immune status</td>
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<td></td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Biologics</td>
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<tr>
<td></td>
<td>Medications</td>
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<td></td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Prosthetic devices</td>
</tr>
<tr>
<td></td>
<td>Dental restorations</td>
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<tr>
<td>Trauma</td>
<td>Burns</td>
</tr>
<tr>
<td></td>
<td>Lacerations</td>
</tr>
<tr>
<td></td>
<td>Poisons</td>
</tr>
</tbody>
</table>
1.4 Oral pemphigus vulgaris

Pemphigus encompasses a group of life-threatening autoimmune diseases that is characterized by circulating IgG antibodies targeting several types of keratinocyte antigens [92]. The term pemphigus is derived from the Greek word *Pemphix*, meaning bubble or blister, introduced by Hippocrates (460–370 BC), who described a pemphigoid fever as “*pemphigodes pyertoī*”, a disease that was not having blisters and accordingly perhaps did not signify pemphigus. The term pemphigus was originally given by Wichmann in 1791, who classified the disease as a chronic bullous disease. Pemphigus vulgaris (PV) was recognized as a separate entity by Lever in 1953, based on its clinical aspects, natural course and histopathology [93]. In 1964, using indirect immunofluorescence (IIF), Beutner and Jordon discovered that the sera of patients with PV had immunoglobulin IgG autoantibodies against the cell surface of keratinocytes [94]. Later in 1990, Amagai et al. [95, 96] identified the intercellular antigen as desmosomal cadherin, desmogleins (Dsg)-3 130-kDa adhesion molecules.

1.4.1 Desmosomes

Oral epithelium is a complex structure consisting mainly of keratinocytes anchoring to one other by desmosomes, and to the underlying basement membrane via hemidesmosomes. Desmosomes are glycoproteins of the cadherin supergene family that serve as adhesive complex as well as a cell-surface attachment site for the keratin intermediate filaments of the cytoskeleton. They comprise series of proteins, mainly Dsg and desmocollins that link to cytokeratins by desmoplakins and plakoglobin [97]. Each protein consists of an extracellular domain, a transmembrane domain, and an intracellular domain. Desmosomes are crucial for intercellular adhesion of oral and skin keratinocytes. However, some differences do exist; Dsg3 is expressed all over the oral epithelium, while it is only expressed in the basal and immediate suprabasal layer of the epidermis. On the other hand, Dsg1 is expressed all over the epidermis and oral epithelium, more in the superficial layers and less in the deeper layers of both
epidermis and oral epithelium [98]. When both desmosomes coexist, damage to any one of them wouldn’t affect the integrity of the epithelium.

1.4.2 Pathogenesis and aetiology

Pathogenesis of PV is not yet completely understood. Acantholysis is the histologic hallmark of PV, and describes separation of keratinocytes from each other. There are several hypotheses about acantholysis in PV that each may contribute partially to explaining its mechanism. In 1999, Amagai et al. [99] proposed the Dsg compensatory mechanism theory, which clarified the basic pathophysiology of pemphigus and the classification of the clinical features. In 2001, Grando et al. [100] hypothesized that anti-Dsg autoantibodies do not act alone to cause pemphigus. Rather, other autoantibodies which accompany antibodies directed against Dsg1 and 3, play essential roles in the development of the disease. In 2004, Wang et al. [101] suggested that apoptosis may play a significant role in the mechanism of acantholysis. In 2006, Claude et al. [102] proposed the basal cell shrinkage hypothesis. It was based on existing sharp differences in the cytoskeleton composition of basal and suprabasal keratinocytes, as well as differences in surface receptors. Accordingly, there are differences in their rigidity and signaling events that are triggered by PV antibodies. Recently, Grando et al. [103] proposed a new term, apoptolysis, which is suggested to be the link between suprabasal acantholysis and cell-death pathways to basal cell shrinkage.

Although the PV autoantibodies are pathogenic, the role of cellular immunity system in the acantholysis is unclear. Studies have shown that autoreactive T-cell responses to Dsg3 may be crucial in the pathogenesis of PV, since antibody production generally required T-cell help. In addition, a strong association was found between specific HLA class II alleles and recognition of Dsg3 by T lymphocytes [104].

Although pemphigus has been reported in all races and ethnic groups, a significantly increased prevalence of PV has been observed in certain ethnic groups such as Ashkenazian Jews, Mediterranean descendants and persons from South Asia [105-
Rare familial cases of PV have been reported [108]. A genetic susceptibility to pemphigus was first proposed by the finding of an increased frequency of major histocompatibility complex class II genes HLA -A10 haplotype in patients with pemphigus [109]. There is also an association with HLA class II allele; (HLA-DR4 (DRB1*0402) in Ashkenazi Jews, DRw14 (DRB1*1041) and DQB1*0503) in Europeans and Asians [110, 111].

In addition, a wide variety of drugs and dietary factors has been implicated in the onset of pemphigus. These may be categorized according to their chemical structure in thiol and non-thiol compounds [112-114]. The role of estrogens [115], radiotherapy [116] cosmetics [117] and viruses (herpes viruses, human herpes virus 8, cytomegalovirus, Epstein Barr virus, HIV) in the etiology of PV is reviewed elsewhere [118]. No infectious pathogen has been proven to date to have an etiological role in pemphigus. PV may occasionally be associated with other autoimmune disorders such as rheumatoid arthritis, myasthenia gravis, lupus erythematosus and pernicious anaemia [119].

1.4.3 Oral lesions

Clinically, pemphigus manifests itself with cutaneous or mucosal blisters and erosions that are distributed according to regional variation of the pemphigus antigen, depending on the kind of epithelial antigen targeted [120]. Thus axilla, scalp, buccal mucosa and face are the principal locations, followed by neck and shoulder, leg, upper back, chest and abdomen, groin, low to mid back, in descending order of frequency. It was originally thought that clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile [121] (Table 4). Recently, it has been demonstrated that Dsg1 and Dsg 3 cannot differentiate between various morphologic subtypes of PV [122] and that pemphigus sera contain autoantibodies to over 50 types of antigens to desmosomal and non-desmosomal adhesion molecules other than Dsgs, not all being pathogenic [123].
Table 4: Main types of pemphigus involving the oral mucosa. Table adapted from Scully & Mignogna [124].

<table>
<thead>
<tr>
<th>Variant</th>
<th>Oral lesions</th>
<th>Antigens localisation</th>
<th>Target Antigens</th>
<th>Antibody Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal PV</td>
<td>Common</td>
<td>Desmosomes</td>
<td>Dsg3</td>
<td>IgG</td>
</tr>
<tr>
<td>Muco-cutaneous PV</td>
<td>Common</td>
<td>Desmosomes</td>
<td>Dsg3 &amp; Dsg1</td>
<td>IgG</td>
</tr>
<tr>
<td>IgA pemphigus</td>
<td>Common</td>
<td>Desmosomes</td>
<td>Dsg3, Desmocollin 1, Desmocollin 2</td>
<td>IgA</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>Common</td>
<td>Desmosomes or Hemidesmosomes</td>
<td>Desmoplakin 1, Desmoplakin 2, Periplakin BP 230</td>
<td>IgG or IgA</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>Uncommon</td>
<td>Desmosomes</td>
<td>Dsg1</td>
<td>IgG</td>
</tr>
</tbody>
</table>

PV is the main and the most prevalent and aggressive type of pemphigus, corresponding to about 70% of cases and the one that usually affects the oral mucosa [124, 125] (Appendix 10.5 depicts clinical manifestations in patients with oral PV in our study). Ninety percent of patients with PV will develop oral lesions during the course of their disease, while a small group of patients never develops skin lesions. Despite the frequency of oral involvement and the fact that oral mucosa could be the primary site of involvement in 75% of cases [126], few studies have investigated the oral manifestations of PV (Table 5). The damage to Dsg3 can be compensated for by Dsg1, which would maintain the integrity of the skin, but not the oral mucosa, particularly in the early stages. This may explain why oral lesions in most cases preceded skin lesions (Dsg compensatory theory) [99].

The clinical manifestations of pemphigus have been quantified and translated to objective outcome measures to assess the disease activity. Such measures are used alongside subjective assessment of disease severity. Accordingly, several clinical outcome measures have been developed to assess the clinical disease activity and disease progression over time and to evaluate therapeutic intervention [127, 128].
only validated ones are the autoimmune bullous skin disorder intensity score (ABSIS) and the pemphigus disease area index (PDAI) [129]. Many authors have found that the clinical severity of pemphigus has a parallel relationship with the level of Dsg1 and Dsg3 antibodies in the patient’s serum [130-132], a result that has great impact in treatment plan and patients follow up, but conflicting results do exist [131, 133].
Table 5: Summary of studies that have investigated more than three patients with oral lesions of pemphigus vulgaris

<table>
<thead>
<tr>
<th>Year/Country</th>
<th>Type of study, place of study</th>
<th>Mean age (range years)</th>
<th>No. of patients</th>
<th>Female/Male</th>
<th>Oral mucosal sites in descending order</th>
<th>Patients with non-oral mucosal sites N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[134] 1997 USA</td>
<td>Retrospective Dental clinic</td>
<td>42 (3-66)</td>
<td>12</td>
<td>9/3</td>
<td>Gingiva, buccal, tongue, palate, floor of mouth, labial, oropharynx</td>
<td>8 (66.6%)</td>
</tr>
<tr>
<td>[135] 1999 UK</td>
<td>Retrospective Dental clinic All patients over the previous decade 1997</td>
<td>50.2 (16-83)</td>
<td>55</td>
<td>33/22</td>
<td>Buccal, palate, tongue, lip, gingiva, floor of mouth</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>[136] 2000 USA</td>
<td>Retrospective Dental clinic</td>
<td>56.1 (27-68)</td>
<td>42</td>
<td>30/12</td>
<td>Buccal, gingiva, palate, tongue</td>
<td>Not recorded</td>
</tr>
<tr>
<td>[137] 2001 USA</td>
<td>Retrospective Dental clinic (biopsies) 1974-1996</td>
<td>56.5 (27-79)</td>
<td>33</td>
<td>25/8</td>
<td>Buccal, mandibular vestibules, entire mucosa, tongue, palate</td>
<td>1 at examination 1 history of skin lesion</td>
</tr>
<tr>
<td>[138] 2005 Spain</td>
<td>Retrospective Dental clinic 1981-2001</td>
<td>44.7 (21-87)</td>
<td>14</td>
<td>10/4</td>
<td>Cheek, lip, gum, palate</td>
<td>6 (42.8%)</td>
</tr>
<tr>
<td>[139] 2006 Thailand</td>
<td>Retrospective Dental clinics 1991-2004</td>
<td>37.7 (18-55)</td>
<td>18</td>
<td>12/6</td>
<td>Gingiva, buccal, palate, retromolar area, tongue, lip, floor of mouth</td>
<td>Not reported</td>
</tr>
<tr>
<td>[140] 2007 India</td>
<td>Retrospective Dental clinic 2004-2006</td>
<td>42.3 (20-69)</td>
<td>20</td>
<td>12/8</td>
<td>Buccal, palate, lip, tongue, floor of mouth, tonsil, gingiva</td>
<td>Not reported</td>
</tr>
<tr>
<td>[106] 2007 Greece</td>
<td>Retrospective Dental and dermatology clinic 6th decade of life (30-83)</td>
<td>129</td>
<td>88/41</td>
<td>Not recorded</td>
<td>18 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Country</td>
<td>Study Type</td>
<td>Time Period</td>
<td>Age Range</td>
<td>Cases</td>
<td>Number</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------------------------------------</td>
<td>----------------------</td>
<td>-----------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>1985-2004</td>
<td>India</td>
<td>Retrospective Dental and dermatology clinic 2001-2007</td>
<td>42.7 (15-70)</td>
<td>71</td>
<td>45/26</td>
<td>Buccal, palate, lip, tongue, floor of mouth, gingiva</td>
</tr>
<tr>
<td>2000-2006</td>
<td>Croatia</td>
<td>Retrospective Dermatology clinic 2000-2006</td>
<td>(20-95)</td>
<td>15</td>
<td>10/5</td>
<td>Buccal, palate, gingiva, tongue, lip</td>
</tr>
<tr>
<td>2007-2008</td>
<td>Brazil</td>
<td>Cross-sectional Dermatology clinic 2007-2008</td>
<td>(5-88)</td>
<td>6</td>
<td>3/3</td>
<td>Buccal, palate</td>
</tr>
<tr>
<td>1988-2009</td>
<td>Brazil</td>
<td>Retrospective (biopsies) 1988-2009</td>
<td>3rd-5th decades of life</td>
<td>22</td>
<td>17/5</td>
<td>Buccal, palate, lip, retromolar area</td>
</tr>
</tbody>
</table>
1.4.4 Microscopic appearance

Histologically, the oral lesions of pemphigus show a pattern analogous to that studied in skin lesions. The early alteration in the lesion is intercellular edema within the lower epithelium, followed by detachment of epithelial cells (acantholysis) due to loss of intercellular bridges, which is typical in pemphigus, but may also be seen in viral diseases, Darier’s diseases and others [93, 119, 146]. Consequently, a horizontal cleft develops above the basal cell layer, where basal cells stay attached to the basement membrane and are separated from one another (tombstone). The acantholytic cell (Tzanck cells) are detected after attachment loss within the cleft and show degenerative changes characterized by large, swollen, hyperchromatic nuclei and little cytoplasm [147]. Polymorphonuclear leukocytes may also be present within the cleft. In the early stage of the disease, eosinophils may be detected in the lower epithelium, a finding referred to as eosinophilic spongiosis [148]. Slight perivascular mixed inflammatory cell infiltrate found in the underlying connective tissue, often including eosinophils.

For diagnostic confirmation, the histopathology alone may not be enough, so the immunofluorescence technique is important. Since 1964, IIF of serum has been used to identify circulating autoantibodies and to quantify the autoantibody concentration by using different substrates, such as human skin or monkey esophagus [94]. In some patients, pemphigus antibodies are not detected due to interference by other antibodies, the presence of immune complexes, early stages of disease or when the disease is inactive. In such cases, direct immunofluorescence (DIF) is the most reliable test for pemphigus. It is performed on fresh tissue and demonstrates the presence of intercellular IgG and C3 along the cell surface membrane. A more sensitive test than IIF, enzyme-linked immunosorbent assay (ELISA), is also used to detect circulating autoantibodies to Dsg1 and Dsg3 [130]. These methods require fresh tissue or serum. Several studies have used formalin-fixed paraffin embedded tissue as an alternative to frozen tissue, and have reported the possibility of detecting pemphigus autoantibodies...
intercellularly when using DIF[149], immunoperoxidase staining technique [150] and when using IHC [151].

1.4.5 Treatment

Before the introduction of steroid therapy in the late 1940s, PV was always fatal, with dehydration and secondary systemic infections as the main causes of death [152-154]. Based on global literature published in the past 12 years, the PV mortality rate was 8.2% (range 0-20%) with an annual rate of mortality of 0.6% [123]. The mortality rate was much lower when the disease was confined to the mouth, but high doses and prolonged administration of steroids can result in numerous adverse effects, many of which are serious or even life threatening [155].

The current therapeutic regimen is based on systemic corticosteroids along with other adjuvant therapy, such as immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, chlorambucil, and methotrexate). Anti-inflammatory drugs and immunomodulation therapy have also been introduced in unresponsive cases. Recently, a biological therapy named rituximab has been introduced and proven to be highly effective in the treatment of severe and recalcitrant pemphigus since earliest report [156]. Rituximab is a human/murine chimeric monoclonal antibody directed against CD20 of B-cells. It reduces circulating B-cell and prevents their maturation into antibody-producing plasma cells.
1.5 Psycho social impacts of OML

In 1947, the WHO declared a new definition of health in terms of a state of complete physical, mental, and social wellbeing and not only the absence of disease and infirmity [157]. This new health concept acknowledged that objective measures of diseases in terms of clinical indicators alone should be extended to encompass individuals’ subjectively perceived oral health status. Quality of life (QoL), a concept that has been recognized to be part of a broader health concept, has been defined as “individuals’ perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns” [158]. QoL is now recognized to be an important adjunct to the traditional clinical measures of health, including oral health [158]. In an effort to make QoL more useful for health researchers, health related quality of life was borne as a new concept in the 1960s. Bowling [159] stated that “health-related quality of life (HRQoL), is a major concept in relation to the experience of illness and the outcome of health services”. The notion of oral health-related quality of life (OHRQoL) appeared in the 1980s without any strict definition and thus should be based on the same reasoning as the HRQoL. Nevertheless, a fluid definition has been accepted in terms of “cyclical and self-renewing interaction between the relevance and impact of oral health in everyday life” [160]. OHRQoL is not only about individuals’ self-perceived oral health in terms of social, psychological and functional consequences of oral diseases, but also about their perception on how important those consequences are. The most important aspect of OHRQoL is to bring the individual rather than only the teeth/mouth perspective into focus in the research field of oral health [161].

1.5.1 Measures of oral health related quality of life

A number of OHRQoL measures have been developed and used in different clinical settings, oral health surveys and clinical trials [162]. Principally, there are three categories of OHRQoL measure; societal indicators, global self-ratings of OHRQoL (single-item ratings) and multiple item inventories OHRQoL [161]. These measures
were suggested to be used as supplements to the traditional clinical oral health indicators, to expand communication between patients and their health workers and to offer meaningful information of the psychosocial consequences of oral diseases [163]. Table 6 depicts some of the OHRQoL instruments developed for use in adults, their original reference, abbreviations and the number of items included.
Table 6: Oral health related quality of life instruments for use in adults, their original reference, abbreviations, and number of items included

<table>
<thead>
<tr>
<th>Original Reference</th>
<th>Instrument</th>
<th>Abbreviation</th>
<th>No. of items</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>[166] Atchison &amp; Dolan (1990)</td>
<td>Geriatric (General) Oral Health Assessment Index</td>
<td>GOHAI</td>
<td>12</td>
<td>Generic</td>
</tr>
<tr>
<td>[167] Dolan et al. (1991)</td>
<td>Rand Dental Health Index</td>
<td>-</td>
<td>3</td>
<td>Generic</td>
</tr>
<tr>
<td>[170] Locker &amp; Miller (1994)</td>
<td>Subjective Oral Health Status Indicators</td>
<td>SOHSI</td>
<td>42</td>
<td>Generic</td>
</tr>
<tr>
<td>[173] Cornell J et al. (1997)</td>
<td>Oral Health Quality of Life Inventory</td>
<td>OH-QoL</td>
<td>56</td>
<td>Generic</td>
</tr>
<tr>
<td>[176] Cunningham et al. (2000)</td>
<td>Orthodontic Quality of Life Questionnaire</td>
<td>OQLQ</td>
<td>22</td>
<td>Specific</td>
</tr>
<tr>
<td>[177] McGrath &amp; Bedi (2001)</td>
<td>UK Oral Health Related Quality of Life Measure</td>
<td>OHQoL-UK</td>
<td>16</td>
<td>Generic</td>
</tr>
<tr>
<td>[179] Ni Riordain et al. (2011)</td>
<td>Chronic Oral Mucosal Diseases Questionnaire</td>
<td>COMDQ</td>
<td>26</td>
<td>Specific</td>
</tr>
</tbody>
</table>
The different OHRQoL measures vary in terms of dimensions measured, format and number of questions, subscales, response format and approaches of acquisition scores. They were imposed to be efficient, easy to complete, and handle, reliable, valid, discriminative, evaluative instruments and supported by a relevant conceptual model [180]. A number of them have been systematically tested to assess their psychometric properties such as reliability, validity and responsiveness [180]. Nevertheless, no single instrument can be viewed as a gold standard set of questions or concepts [181]. The majority of these measures has been constructed in the English language and is planned for use in English speaking countries. Evidence shows that cultural groups vary with respect to OHRQoL, in disease expression and in their use of health care system across countries [182, 183]. Therefore, a systematic approach to translation and cross-cultural adaptation is a first step to choosing an appropriate measure.

The OHRQoL measurements can be divided into generic and disease specific measures. The generic ones evaluate total impact of various oral conditions and are used when comparing OHRQoL across populations, such as Oral Impact on Daily Performance (OIDP) [175]. The disease specific ones, as Orthognathic Quality of Life Questionnaire (OQLQ) [176], focus on unique aspects of the disease being studied and are more responsive to small clinical changes that may occur over time. It has been suggested that both measurements should be used when assessing quality of life [176, 184].

OHRQoL measures principally focus on dental diseases, hyposalivation, dentofacial deformity and temporomandibular disorders [185-188], but few studies have documented the effect of OML upon quality of life [189-193]. Table 7 gives an overview of studies that have focused on the impact of OML on OHRQoL in adults.
Table 7: An overview of studies published globally, focusing on the impact of OML on QoL in adults

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>OML</th>
<th>Study type</th>
<th>Quality of life measure used</th>
</tr>
</thead>
<tbody>
<tr>
<td>[201] (2009)</td>
<td>RAU</td>
<td>Treatment</td>
<td>OHIP-14</td>
</tr>
<tr>
<td>[189] (2009)</td>
<td>OML</td>
<td>Population</td>
<td>OHIP-14, SF-12, GHQ-12</td>
</tr>
<tr>
<td>[203] (2011)</td>
<td>RAU, oral lichen planus, pemphigus vulgaris, mucous membrane pemphigoid, orofacial granulomatosis</td>
<td>Questionnaire/Population</td>
<td>COMDQ, OHIP-14</td>
</tr>
<tr>
<td>[204] (2012)</td>
<td>RAU, oral lichen planus, pemphigus vulgaris, mucous membrane pemphigoid, orofacial granulomatosis</td>
<td>Questionnaire/Population</td>
<td>COMDQ</td>
</tr>
<tr>
<td>[205] (2012)</td>
<td>RAU, oral lichen planus, pemphigus vulgaris, mucous membrane pemphigoid, orofacial granulomatosis</td>
<td>Questionnaire</td>
<td>COMDQ</td>
</tr>
<tr>
<td>[193] (2012)</td>
<td>RAU, oral lichen planus, candidiasis, burning mouth syndrome and paraesthesia, other OML</td>
<td>Questionnaire</td>
<td>OHIP-14, SF-36</td>
</tr>
</tbody>
</table>
Conditions affecting the oral mucosa are often painful disorders, chronic in nature or recurrent, mainly seen in oral medicine or dermatology clinical settings [189, 190, 206, 207]. Many of these conditions are not fatal, but clinical manifestation and treatment options in the management of these conditions may end up in significant morbidity, resulting in psycho-social and functional impacts [162, 208-210]. Hegarty et al. [194] were the first to study the impact of OML upon quality of life by evaluating the performance of the Oral Health Impact Profile (OHIP-14) and OHQoL-UK in patients with erosive lichen planus. The study suggests that these instruments performed well in the management of OML and supports the use of OHRQoL measures in patients with OML, specifically the chronic and the recurrent lesions. Chronic Oral Mucosal Diseases Quality of Life Questionnaire (COMDQ) is the first discipline-specific OHRQoL measure introduced to the field of oral medicine by Ni Riordain et al. [179]. The measure has proven to be valid, reliable and responsive to assess OHRQoL in patients with lichen planus, RAU, oral pemphigus and oral pemphigoid [203]. However, this measure does not allow comparison across diseases.

The OIDP inventory is an OHRQoL instrument widely used to assess impacts that affect individuals’ daily life [175]. This inventory is based on a theoretical framework modified from the WHO International Classification of Impairment, Disabilities and Handicaps (ICIDH) [211] which has been amended for dentistry by Locker [212] (Figure.1). The ICIDH provides bases for the empirical exploration of the links between different dimensions or levels of consequence variables and consists of the following key concepts: impairment, functional limitations, pain, discomfort, disability and handicap. The first level (oral status) includes oral impairments that show the immediate biophysical outcomes of disease, usually assessed by clinical indicators. The second level (intermediate impacts) includes possible early negative impacts caused by oral health status: dissatisfaction with dental appearance, functional limitations, pain and discomfort. The latter two are related to the experiential aspects of oral conditions in term of symptoms. Any of the dimensions mentioned at the first and second level may lead to the third level (ultimate impacts) of outcomes which express any difficulties in performing daily life’s activities. The OIDP focuses on
measuring the third level, corresponding to the WHO and Locker’s concept of disability and handicap [211, 212].

Figure 1: Theoretical framework of consequences of oral impacts (Modified from WHO’s International Classification of Impairment, Disabilities and Handicaps [211])
The OIDP inventory can be used either as a generic or a condition-specific OHRQoL measure. It has proven to be reliable and valid in general population based studies, as well as in studies of patients with specific oral disorders [213-215]. The OIDP provides a significant endpoint outcome scale for oral conditions within a concise, reliable and valid instrument. A cross-sectional study precludes the assumption that a measure proven to be reliable and valid is appropriate for detecting meaningful clinical changes. These changes within individuals could be natural or as a result of clinical intervention. Here, instruments with properties such as responsiveness, longitudinal validity and interpretability are recommended [216]. The first step in selecting an appropriate measure of OHRQoL is therefore to determine clearly the specific objectives of the study, whether they are descriptive, predictive, discriminative or evaluative and the exact purpose of using such a measure [217].

1.6 General and oral health services in the Sudan

At the time of the present study, Sudan had 25 State Ministries of Health (SMoH), one in each State. Within each state, a number of localities (134 in total) are managed through a district health system. The main body; The Federal Ministry of Health (FMoH) is responsible for the development of national health policies, strategic plans, monitoring and evaluation of health systems activities. Under the FMoH we find:

1. **The SMoH** which are mainly responsible for policy implementation, detailed health programming and project formulation.

2. **The district health system** which is responsible for implementing the national health policy through the primary health care concept.

   - **The primary health care**, at village level represents the first level of contact between the community and the health services.
   
   - **Secondary health care** is available in small towns through rural hospitals and urban health systems.
• **Tertiary health care** services comprise provincial, regional, university and specialist hospitals.

Health services are provided through different partners including, in addition to FMoH and SMoH, Armed Forces, Police and Security Forces, Health Insurance Organizations, the Ministry of Higher Education through its university hospitals, civil society and the private sector. The private sector in Sudan has grown substantially during recent years, predominantly in urban areas. It focuses mainly on curative rather than preventive services. Those partners play an important role in filling some of the gaps in coverage of the government system and serving populations. However, all partners act in isolation, due to poorly designed administrative systems for coordination and guidance [218-220]; this creates significant disparity in the referral system and the geographic distribution of health facilities and personnel. In dental health services, the dentist:population ratio in the Northern states of Sudan was 1.8:100,000, while in Khartoum state the ratio was 3.2:100,000 [221]. There were about 1.8 times as many dentists serving the Khartoum state alone than served the remaining population in the Northern states of Sudan. Wide regional variations were still evident in urban areas (1:30,000) versus rural areas (1:130,000) [221, 222]. A similar trend has been found among medical doctors in Northern states of Sudan (35.8:100,000) and in Khartoum state (56.5:100,000). In the dermatology field, the ratio of dermatologists to population was 0.4:100,000, with the majority based in Khartoum state [221].

Before the early 1990s, health services were provided free of charge, but after that time the government has introduced user fees. The National and Social Health Insurance Corporation have been implemented in response to the impact of the financial reform policy and the introduction to the used fees in public facilities. The insurance companies cover most of basic medical services expenses as well as the basic dental procedures [220]. Total health expenditure as a proportion of Gross Domestic Product (GDP) was 6%, and out-of-pocket health expenditure from the total health expenditure was 64.3% [221].
There is a deficiency in the available information regarding standardized referral protocols and coordination between oral health and general health system in Sudan, in particular the dermatology and oral health schemes.

1.7 Justification

Sudan is a country with striking diversity in all aspects. The epidemiological profile of the country is typical of sub-Saharan African countries; malnutrition and communicable diseases dominate the health scene with high vulnerability to outbreaks of disease [223]. Whilst general health is well documented, little is known about oral health in the Sudanese population. There is a lack of studies regarding the frequency, distribution and psycho-social consequences of OML as well as studies addressing clinical and histological features of oral pemphigus in the Sudanese population.

This is a concern because many skin lesions that are highly associated with oral lesions could be misdiagnosed by the dentist due to lack of information or improper examination [224]. Although the dentist is often the first health professional to be consulted by patients who develop acute oro-facial symptoms of different systemic diseases and various other lesions and infections, this has not received adequate attention.

KTH is the largest national referral hospital in Sudan. It receives patients from all over the country and is located in the most densely populated area in Sudan, Khartoum state. It has a high number of patients who present with various oral manifestations. The importance of the diagnosis of oral conditions in dermatology has been underlined due to the frequency and diversity of oral lesions. For the moment, no clear strategy has been developed for the management of such cases at any hospital in Sudan. Therefore, improving knowledge about the frequency and diversity of OML at the dermatology clinic will strengthen and enhance interdisciplinary and multispectral approaches, as opposed to a single sector approach in the management of such patients.
The clinical diagnosis of OML may provide a signal about its cause and prognosis, but may fail to indicate the level of impairment that will follow. Studies have shown that OML negatively affects oral health quality [189, 190].

OML is a significant public health problem, since some are life-threatening and others have great impact on individuals and society in terms of pain, discomfort, social and functional limitations. The significance of evaluating the Sudanese skin disease patients’ own perceptions of the impact of their oral health on daily living has not been investigated.
2. Aims of the study

2.1 General aim

The overall aim of this study was to contribute new information regarding the frequency, socio-behavioural distribution, socio-psychological consequences and clinical and histopathological features of oral mucosal lesions in patients with skin disease in the Sudan. This information is crucial for determining the magnitude, risk indicators and burden of such diseases and provides data essential for formulating health policy in order to meet the health care needs of patients.

2.2 Specific objectives

- To estimate the frequency, diversity and socio-behavioural correlates of different types of OML in adult patients with dermatological diseases (Paper 1).

- To assess the relationship between oral health related quality of life (OHRQoL), OML and reported oral symptoms, perceived general and oral health conditions and caries experience (Paper II).

- To evaluate the clinical and histological characterization of oral pemphigus lesions, and to assess the diagnostic significance utility of the light microscope in patients with pemphigus along with IHC examination, using the patient’s formalin-fixed, paraffin-embedded oral tissue biopsy specimens (Paper III).
3. Materials and methods

3.1 Study area

This thesis is based on a study conducted in KTH dermatology outpatient clinic. The study took place before the referendum in January 2011. At the time of the study, Sudan was the largest country in Africa and it bordered the Red Sea and nine other African countries. The total land area was 2.6 million square kilometres, extending from latitude 4 to 22 degrees North and from longitude 22 to 38 degrees East. Sudan was a multiethnic multicultural country. However, two major and distinct ethnicities prevailed – Arab (north) and African (south) – with hundreds of ethnic and tribal divisions and languages. The environment in Sudan ranged from tropical damp and rainy in the south, to desert and savannah in the central and northern areas [201, 202]. At the study time, Sudan had 25 states; Khartoum state was the most densely populated and had an area of 22,122 square kilometres, with population rapidly exceeding 6 million, including over 2 million internally displaced persons from the Southern war-affected zone as well as Western and Eastern war or drought-affected areas. Khartoum city, the national capital of Sudan, was the capital of Khartoum state [218].
Quick facts about Sudan population before January 2011 [220, 225, 226]

- Population; 41,406,498 (the Southern region has a population of around 8 million and was predominantly rural) [221].
- Males accounted for 51.3% with nearly the same proportions in Khartoum state [221].
- Population living in urban areas: 44%.
- Population < 15 years: 42.6% [221].
- Population > 60 years: 5.3% [221]
- Annual population growth rate: 0.2%.
- Life expectancy at birth; 59 years.
- Infant mortality rate (< 1 year old): 66/1000 live births.
- Literacy: 61.1%.
- Religions: Islam (official), Christianity and indigenous beliefs (Southern Sudan)
- Languages: Arabic (official), English (official), tribal languages e.g.: Nubian, Beja, Fur, Nuban, Ingessana, etc.
- Work force: agriculture: 80%; industry and commerce: 7%; government: 13%.

3.2 Study population and study group

In the present study, the target population consisted of outpatients attending KTH dermatology department, in Khartoum city. The KTH is a tertiary health care service and is the oldest and largest national and teaching hospital in Sudan. It is an open
public and referral hospital receiving patients from Khartoum state and other parts of Sudan. The patients’ socio-economic status is mainly low and middle class.

3.3 Study design

To achieve the specific objective of this project, a cross-sectional hospital-based study was carried out focusing on patients aged 18 years and above attending the outpatient dermatologic clinic at KTH from October 2008 to January 2009.

3.4 Sample size calculation

The required sample size was calculated separately for each specific objective of the present study. The largest sample size attained was presumed to be satisfactory and implemented for the whole study. The sample size that was necessary for estimating the prevalence of oral manifestations in patients with skin diseases was assumed satisfactory and adopted. It was based on common skin lesions that were seen in the KTH; lichen planus, eczema and psoriasis (reported by consultant dermatologist dermatologist Adil Bashir). A minimum sample size of 500 patients was calculated based on an assumed prevalence of OML in skin disease patients of 5%, a confidence interval (CI) of 95%, and an absolute precision of 0.02 (i.e. standard error). Complete data and consent were available for 588 patients (588/1540, 38.1%). The sample profile is depicted in Figure 2.
The material for these studies is based on three different phases detailed below. Information regarding the three phases was collected in one main survey (one visit only for each patient) which constitutes the baseline data for the three papers reporting on this study.
3.5 Interview

Phase 1

A structured interview schedule including questions regarding socio-demographics, health and oral health related behaviours and OHRQoL was initially constructed in English, translated to Arabic (the official language of Sudan) and then translated back into English (Appendix 1). Sensitivity to culture and selection of appropriate words were considered. OHRQoL was assessed using the Arabic version of the eight item OIDP frequency inventory (Appendix 2). Interviews were administered in face to face settings by two trained dentists. The interviews were conducted in the Arabic language and were pilot tested before being used in the field.

Phase 2

An expert dermatologist (Dr Hussein Salman) evaluated each patient’s dermatological diseases through information obtained in a structured interview conducted in the outpatient department of the dermatology clinic (Appendix 3).

3.6 Clinical oral examination

Phase 3

A full mouth clinical oral examination was conducted in accordance with the WHO criteria for diagnosis of OML [48] by one trained and calibrated dentist, Nada M. Suliman. Full details of the oral examination are provided in Paper I. Caries experience was assessed under field conditions and scored according to the criteria described by the WHO [227]. Decayed, missing and filled teeth (DMFT) index was computed as the sum of decayed, missing and filled teeth. Clinical parameters were recorded using a structured questionnaire modified from the WHO assessment form for oral mucosal diseases [48, 227] (Appendix 4). In those cases requiring further examination, diascopy, smears for Candida albicans, and punch or incision biopsies were
performed. Smears were taken of lesions suspected of being candidiasis and sent immediately to Sudan National Laboratory, Khartoum, where they were processed.

3.7 Oral tissue biopsies

Biopsies were obtained from lesions where diagnosis was uncertain by clinical examination. The Minor operation room in the dermatology outpatients department was used to perform biopsies. Only 12% (n=70) of the patients agreed to undergo biopsy. To obtain lesion and peri-lesion biopsies, punch biopsies (diameter 6 mm) and incisional biopsies were performed under lidocaine local anaesthesia. For vesiculobullous lesions, punch biopsies were taken from normal-appearing intact oral mucosa, close to the lesion. Immediately, the specimens were kept in tubes filled with 10 % buffered formalin and labelled with subject’s code number, date, and location. The formalin: specimen ratio was 10:1. The wounds were closed with 0/3 silk suture material, and patients came back after one week for suture removal. All tissue specimens were embedded in paraffin, sectioned, and routine stained with Hematoxylin and Eosin (H & E) at the Gade institute, University of Bergen, Norway. Furthermore, selected sections were stained for examination of Candida albicans or melanin. IHC examination was performed on formalin-fixed, paraffin-embedded oral PV tissue specimens by an expert technician (Edith Fick).

Final diagnoses of all lesions were confirmed by an expert oral pathologist (Anne C. Johannessen). Skin lesions and OML encountered during the data collection, were photographed using a digital camera (Canon EOS 400D).

3.8 Procedure for immunohistochemistry on formalin-fixed paraffin embedded oral tissue

Formalin-fixed paraffin embedded tissue from 11 oral tissue biopsies were used. Sections, 4µm thick, were cut and mounted on glass slides (Super Frost Plus) and
heated at 56 °C overnight. The sections were deparaffinized in xylene and rehydrated in alcohol. For C3c, sections were incubated in target retrieval solution (pH6, DAKO, Glostrup, Denmark S1699), microwaved for 15 minutes after the buffer had come to a boil, then allowed to cool down on the bench and then washed slightly under running tap water for 5 minutes. Primary anti-human C3c polyclonal rabbit Compliment (DAKO, A0062) at a dilution of 1:15000 were incubated for 30 minutes at room temperature. For IgG, sections were incubated in epitope retrieval solution (proteinase type XXIV bacterial, Sigma P 8038 37) for 10 minutes at 37 °C. Primary antibody polyclonal Rabbit Anti-Human IgG, (A 0423) at a dilution of 1:60000 were incubated for 60 minutes. Endogenous peroxidase activity was blocked by 0.03% hydrogen peroxide (H2O2) for 7 minutes. Detection was performed using Peroxidase labeled polymer conjugated to goat anti-rabbit immunoglobulin (Envision + DAKO, K5007) for 30 min. Between each of the above steps, sections were washed with Tris-Buffered Saline with Tween (TBST, pH 7.6, DAKO S3306) for 10 minutes. The reaction was then visualized using 3, 3’- Diaminobenzidine (DAB). The sections were counterstained with hematoxylin, dehydrated and mounted with a non-aqueous mounting medium (Eukitt; O.Kindler GmbH & Co., Freiburg, Germany).

3.9 Diagnostic criteria for oral mucosal lesions

An OML was defined as any abnormal change or any swelling on the oral mucosal surface. Diagnostic criteria for OML were based on Axéll’s criteria and those defined in previous studies and reviews [22, 48, 228, 229].

3.10 Data characteristic and Statistical analysis

- Data for Papers I and II were extracted from the main study group (n = 588). The target population was patients with a confirmed diagnosis of skin diseases (n = 544). The population was divided into three groups, patients with, without, and with ≥ 2 OML. The frequency was obtained from the whole population (n = 544),
from the population diagnosed with OML (n = 315), and from each group of OML defined in the study. OHRQoL was assessed in patients without OML, with one, and with more than one OML.

- Material for Paper III was generated from the total study group (n = 588). The study group was patients with oral pemphigus.

- Data analyses were carried out using PASW Statistics version 18.0 (SPSS Inc., Chicago). The significant level was set at 0.05 with 95% confidence interval.

*Table 8: Statistical tests and methods used in Paper I, II, and III*

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<th>Statistical tests/methods used</th>
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3.11 Ethical considerations

The research complied with the Helsinki Declaration and requirements for ethical clearance, and approval letters were obtained by the participating institutions’ ethics committees (University of Science and Technology (UST) and KTH, Department of Dermatology) in Sudan. In Norway, the ethical approval was obtained from the Regional Committee for Medical Research Ethics of Western Norway (3.2008.1434). The patients were verbally informed about the study and received fully documented information regarding the study and that they could decline to participate or withdraw at any time without negative consequences, after having given consent. Written informed signed consent or finger print for participation and publication of the study was obtained from patients or their parents or guardians. Confidentiality of the patients’ data was maintained, participants were informed about their oral conditions and health education was provided. Those who needed dental services were referred to the UST, Faculty of Dentistry, for further investigation and management.
4. Results

4.1 Paper I: Oral mucosal lesions in patients with skin disease attending a dermatologic clinic: a cross-sectional study in Sudan

Results: A total of 57.9% (315/544) of the patients were diagnosed with at least one clinically recognized type of OML. Sex was associated significantly with OML (63.2% men versus 52.6% women, p<0.05). Among the 14 groups of OML recognized in the study, tongue lesions were the most frequently diagnosed group (23.3%), followed in descending order by white lesions (19.1%), red and blue lesions (11%) and vesiculobullous diseases (6%). White lesions and ulcerative conditions occurred most frequently in older patients and men, respectively, p<0.05. OML was most often associated with the skin diseases vesiculobullous reaction pattern (72.2%), lichenoid reaction pattern (60.5%), infectious lesions (56.5%), psoriasiform reaction pattern (56.7%), and spongiotic reaction pattern (46.8%). Tongue lesions were the most frequently occurring OML group across the various skin diseases, registering the highest prevalence among psoriasiform reaction pattern. OML in patients with skin disease was most frequently observed in older age groups (62.4% older versus 52.7% younger, p<0.05), in patients with a systemic disease (65.2% with systemic versus 51.9% without systemic disease, p<0.05) and among current users of smokeless tobacco (toombak) (77% current use versus 54.8% no use, p<0.00).

4.2 Paper II: Oral health related quality of life in a Sudanese dermatologic clinic: influence of oral mucosal lesions and oral symptoms: a cross sectional study

Results: The Arabic version of the OIDP inventory maintained the overall concepts of the original English version and showed acceptable reliability in terms of Cronbach’s
alpha coefficient of 0.89 in the study group, and in the separate groups (0.81, no OML), (0.89, one type of OML) and (0.92, > one type of OML). A total of 35.6% (190/544) patients reported at least one OIDP (Mean OIDP total score 11.6, sd = 6.7). The prevalence of caries experience was 89.9%, oral symptoms 84.4%, and systemic health conditions 45.5% in the whole study population. The prevalence of any oral impact was 30.5%, 36.7% and 44.1 % in patients with respectively no OML, one type of OML and more than one type of OML. Numbers of types of OML and number and types of oral symptoms were consistently and positively associated with higher OIDP scores. Patients who reported bad oral health, ≥ 1 dental visit, patients with ≥ 1 type of OML, and patients with ≥ 1 type of oral symptoms were more likely than their counterparts in the opposite groups to report any OIDP. The odds ratios (OR) were respectively, 2.9 (95% CI 1.9-4.5), 2.3 (95% CI 1.5-3.5), 1.8 (95% CI 1.1-3.2) and 6.7 (95% CI 2.6-17.5). Vesiculobullous and ulcerative lesions of OML disease groups discriminated statistically significantly between subjects with and without OIDP.

4.3 Paper III: Clinical and histological characterization of oral pemphigus lesions in dermatologic patients: a cross sectional study from Sudan.

Results: Twenty-one patients were diagnosed with pemphigus vulgaris (PV), 19 of them (mean age: 43.0; range: 20 - 72 yrs.) presented with oral manifestations (ulcers or erosions). Pemphigus foliaceus was diagnosed in one patient. In PV, female: male ratio was 1.1:1. Missing information occurred in some categories: the majority of the patients were < 50 years old (68.4%, 13/19), low education (84.2%, 16/19), married (77.8%, 14/18), had outdoor jobs (52.6%, 10/19), and resided outside Khartoum state (57.9%, 11/19). Use of toombak was reported by 11.1% (2/18), smoking by 21.0% (4/19) and alcohol use by 10.5% (2/19). Buccal mucosa and hard palate were the most commonly affected sites. Exclusively oral lesions were detected in 14.2% (3/21). In patients who had experienced both skin and oral lesions during their life time, 50.0% (9/18) had oral mucosa as the initial site of involvement, 33.3% (6/18) had skin as the
primary site, and simultaneous involvement of both skin and oral mucosa was reported by 5.5% (1/18). Oral lesion activity score was higher in those who reported living outside of Khartoum, were outdoor workers and had lower education and belonged to central and Western tribes compared with their counterparts. Histologically, all tissues except one had suprabasal cleft and acantholytic cells. By IHC, IgG and C3 were demonstrated intercellularly in the oral epithelium.
5. Discussion

5.1 Methodological considerations

5.1.1 Study design

The data used in these reports were collected in a cross-sectional hospital based study. Data were collected by face-to-face interviews, oral clinical examination, and smears and biopsies in cases of a clinically uncertain diagnosis. The studies were designed to estimate the prevalence and socio-behavioural distributions of OML and the oral impacts of daily performances in patients with skin disease aged ≥ 18 yr. attending the KTH dermatology department, in Khartoum city. The study was also designed to describe clinical and histological features of oral pemphigus vulgaris.

Cross-sectional studies are used to describe the prevalence and socio-behavioral distribution of oral diseases and other oral health related characteristics. Risk indicators, outcomes and confounders of oral conditions are measured concurrently, which implies difficulty to determine whether the exposure precedes or follows the outcome. Nevertheless, cross sectional studies can be used to generate hypotheses about risk factors that should be tested in subsequent longitudinal prospective studies.

Estimates derived from cross-sectional studies are subject to various sources of error, which may bias the results and conclusions presented [230]. Bias is any systematic error in the data and there are two major categories: selection bias and information bias [231]. Selection bias stems from the study participants, for instance selective non-response, whereas information bias stems from errors in the information collected from participants, such as recall bias, socially desirable responses and misclassification. In general, cross-sectional studies are characterized by high probability of recall bias, medium selection bias, medium cost and medium time required compared with other types of observational study [231]. The separate reports have discussed in detail the
methodological problems associated with the present design. In the following section, some of the most important limitations are discussed.

5.1.2 Reliability

Reliability concerns the degree of consistency or repeatability with which an instrument measures an attribute [232]. It reflects the amount of error, both random and systematic, inherent in any measurement [233]. A reliable instrument should minimize the error component and maximize the true component of a measurement score. An instrument is named reliable when repeated measurements made by it, under constant conditions, give the same result [234].

**Consistency and reliability over time**

To achieve reliable measures, several actions were taken in this study. They comprised training of research assistants, use of pilot studies and repeated checks during the data entry process. Furthermore, all clinical examinations (OML and DMFT) were performed by one trained and calibrated dentist (NMS) to reduce variability in physical and psychological factors that can affect the judgment of examiners with respect to diagnosing OML and scoring DMFT.

To examine measurement consistency of DMFT, intra-examiner reliability (test-retest reliability) was assessed. It measures the degree to which similar outcomes are recorded when using the same test on the same sample on two different occasions. Due to some logistic considerations, test-retest was performed in a group of ten dental assistants. The number of subjects included in the test was lower than the WHO recommendation of at least 20 subjects [227]. Dental assistants were expected to have low caries experience and this was assumed to be remembered by the examiner in retesting the individuals. To overcome these problems, the test-retest reliability was performed at a two week interval. In addition, dental assistants were told not to have any dental treatment before the second examination. It was assumed that the two week interval was too short for clinical changes to take place in their caries experience. This
was supported by a study of knee function that found that retest results at two days were similar to those after two weeks [235]. In the present study, Cohen’s Kappa for DMFT was 1.0, indicating perfect agreement according to Landis and Koch [236, 237]. The high level of agreement might be due to the small sample size and the short interval.

As most OML are quite rare, a calibration process that required replicate examinations was not done. Instead, during the clinical training period in Bergen, the investigator studied clinical photographs of the OML that could be expected to be observed in the field using an atlas of diseases of the oral mucosa [5]. One day before data collection, a test-retest approach was applied on more than 40 photographs of OML, using the same atlas with a time intervals of five hours between each test. The agreement was 100%. The disadvantages of this approach were that photographs only provide a two dimensional view for one stage of the diseases, and the possibility of selection bias through memorizing specific oral diseases. Furthermore, different sources of light, different patient positions and level of cooperation might influence the real nature of the diseases. The approach does provide exposure and training to a wide spectrum of OML that are seen infrequently.

For economical and ethical considerations, test–retest reliability assessments for the structured interview (self-reported data) and OIDP inventory were not conducted.

**Internal consistency reliability**

Internal consistency reliability for the OIDP inventory was assessed using Cronbach’s alpha. This measure assesses correlation (homogeneity) between different items constituting a scale. It is a measure of how well a test addresses different constructs and delivers reliable scores. The more homogeneous the items, the higher the correlation (Cronbach’s alpha), and therefore the more reliable the measure, indicating that the items comprising the scale measure the same underlying concept. Alpha coefficients above 0.80 are rated as exemplary, 0.70 to 0.79 as extensive, and those in the range 0.60 to 0.69 indicate only moderate internal consistency [238].
the 8-item adult-OIDP inventory showed Cronbach’s alpha of 0.89 for the total study group. In the separate groups, Cronbach’s alpha was 0.81 (no OML), 0.89, (one type of OML) and 0.92 (> one type of OML). The values of internal consistency obtained in this thesis indicate exemplary internal consistency.

5.1.3 Validity

There are two main aspects of validity, internal validity and external validity. Internal validity is defined as the degree to which a test is capable of measuring what it is intended to measure [238]. External validity refers to whether findings of the study group can be generalized to a wider population [231].

**Internal validity**

Internal validity is the degree to which the results of an observation are correct for a particular group of people being studied [231]. Examples of systematic errors that constitute a threat to internal validity are misclassifications in clinical registrations and information bias in terms of recall- and social desirability bias in self-reported data.

With regards to OML, a wide range of mucosal conditions has been documented (Appendix 5). Each has distinctive associated aetiological, clinical, and histopathological features, creating a difficult and complex environment when studying more than one lesion. The difficulty lies in the inconsistency of clinical presentations for a given condition, which may differ from early to late stages, as well as discrepancies in the extent, severity, and location of the lesions [47]. This situation leads to an absence of a consensus on clinical diagnostic criteria to be used for epidemiological research. To reduce misclassification in the clinical recordings, Axéll’s diagnostic criteria for OML were used [22] in addition to the WHO guidelines for diagnosis of oral mucosal diseases [48]. The WHO guidelines provide a comprehensive systematic approach to examine the oral mucosa which ensures that all parts of oral cavity are included in the examination. More details and other diagnostic criteria that were used in this study can be found in Paper I.
Oral tissue biopsies of the lesion are the best source of accurate and definite diagnoses of OML [239]. In this study, few participants agreed to have oral tissue biopsies, which may entail the misclassification of a number of lesions. To achieve more accurate diagnoses, mucosal smears were obtained when indicated and analysis was done by the Sudan National Laboratories. With regard to vesiculobullous lesions, punch biopsies were taken from normal oral mucosa immediately adjacent to the lesion. It was possible that the twisting motion used to take the specimen could have displaced the oral mucosa. Nevertheless, the procedure was carried out in uninflamed areas as carefully as possible. The IHC for oral PV biopsies was performed by an expert technician (Edith Fick). Furthermore, an expert oral pathologist (ACJ) acted as a validator and verified all the diagnoses on the basis of the diagnostic criteria, the patients’ clinical photographs, biopsies, and disease history.

Optimal diagnosis of dental caries needs adequate lighting, radiography and a precise dental history to obtain reasons for tooth loss. The oral examinations were carried out under field conditions following the WHO criteria of DMFT for field surveys [227]. Due to the impracticability of using more advanced equipment such as radiography machines etc., underreporting of the dental caries prevalence cannot be ruled out. To overcome misclassification regarding dental caries, the examiner was trained and calibrated before the main study.

In this study, data regarding risk indicators and subjective oral health status were collected by face-to-face interviews. Although personal interviews provide an excellent opportunity for probing and explicative questions, one could argue that the method is expensive, time consuming, sensitive and invasive with regard to personal issues. Thus, social desirability could threat the validity of this approach and socially desired (tooth brushing) and undesired (use of toombak) behaviours might have been over- or under-estimated in this study. To minimize these problems, interviewers received adequate training before data collection. The interview was carried out before the oral examination and patients were informed that confidentiality and anonymity would be preserved. In the field of OHRQoL, studies have shown that impact scores are not
affected by the method of interview administration (i.e. personal interview vs. self-performed questionnaire) [240].

Recall bias is another systematic bias that is associated with participants’ recollection. Patients are more likely to remember past exposure, especially if it is commonly known to be associated with the outcome under investigation. The use of a six month period for the assessment of the adult OIDP inventory might reduce recall bias. Nevertheless, the Sudanese version of adult-OIDP inventory has been used previously and validated in Sudan [241]. Paper II describes in detail the procedure in testing the psychometric properties of the Sudanese version of adult-OIDP inventory used in the present study.

**External validity**

To estimate the prevalence of OML among patients with skin disease in Sudan, the entire adult population of Sudanese with skin disease or a randomly selected representative sample of this population should preferably have been investigated, but this was too demanding of time and money resources to be practical. Considering that KTH is the largest public main referral hospital in Sudan, and assuming that patients attending during the study period do not differ from patients attending other times of the year, the study participants might capture the variety in characteristic of patients with skin disease attending dermatologic clinics in Sudan. As the study participants in these studies came from a cross-sectional hospital based study, conducted in a relatively short period of time, it is difficult to ascertain how representative the participants were, with respect to the adult population of dermatology patients inside or outside Khartoum.

To secure cooperation and to increase the respondents’ motivation to co-operate, detailed full information was delivered verbally and in writing to all patients before examination. Participation was voluntary, and participants were informed that they could withdraw from the study at any time. A bias towards health conscious participants is a well-known problem in studies where participation is voluntary [231]. Differences due to self-selection may have created a discrepancy between the selected
study group that should reflect the study population of interest, and the actual study participants. Although written and verbal explanations were provided to present the purpose of the study, lack of knowledge of OML, and in particular the association between skin and oral diseases, strongly affected the response rate. Another reason for non-response was the HIV test. It was requested that suspected participants should be tested. Fear of taking a biopsy, especially for asymptomatic lesions, was an important reason for refusal to participate and for non-participation. Furthermore, the time taken to accomplish the interview, the oral examination, the photographs and biopsy required about 40 to 60 minutes for each patient. That was too long for patients who had another priority (skin lesion) than our research interest. Nevertheless, lack of information about non-respondents impedes any solid assumption about selection and non-response biases and implies that the results of the present study should be interpreted with caution. More detailed information regarding the representativeness of the study population is found in Paper I.

In the present study, data regarding a tribe’s original location could be questioned. Intermarriage between different tribes is a common phenomenon in Sudan so that a person could be descended from more than one tribe. This was not controlled in our data, and the usual practice in Sudanese culture is to report the father’s tribe. This could lead to misclassification, as a participant could have parents from tribes that originate from two different locations.

5.2 Discussion of the major findings

5.2.1 Prevalence of oral mucosal lesions

Paper I showed that the prevalence of OML among adult Sudanese with skin diseases was 57.9%. This is in accordance with the international literature investigating the prevalence of OML in different settings (25%-61.6%) [23, 24, 42-44, 242]. In contrast, studies from Cambodia and Malaysia have shown a lower prevalence of OML (4.9%
According to our knowledge, there are only two studies of OML in dermatology outpatient clinics. In Mexico City, specialists in oral medicine and oral pathology found that 6% (n=60) of patients that had been referred to a dermatology clinic had oral lesions [206]. The most frequently observed OML in that study were PV (18.3%), lichen planus (8.3%), candidiasis (8.3%) and RAU (6.6%). Another study, conducted by dermatologists in Turkey, reported a prevalence of OML of 22.6% among 1041 consecutive dermatology outpatients [207]. Here, fissured tongue, coated tongue, RAU and linea alba topped the list of the OML identified in that study. In both studies as well as in our present study, discrepancies in outcomes were observed. This might be attributed to variation in examiners, sample size, diagnostic criteria and other methodological issues that have been discussed earlier in the present study.

Among the patients with skin disease investigated in this study, males were more prone than females to have at least one OML. It is likely that the sex differences may be attributed to use of toombak, social responsibility and masculinity [243]. A similar sex difference in OML has also been observed in previous studies [44, 244] but the opposite sex gradient has been reported elsewhere [24]. In our study, the prevalence of OML varied according to age in accordance with findings of some previous studies [44, 242]. Our study also showed that tongue lesion was the most frequently diagnosed OML, amounting to 23%. A relationship between tongue lesions and psoriasis has been postulated for many years. A recent metacentric, observational and controlled study from Italy suggested that fissured and geographic tongue can be considered as oral manifestations of plaque-type psoriasis [245], although the reason for this association is not clear. The present result showed that more than half of the psoriasiform reaction pattern group had tongue lesions, with fissured tongue being the most prevalent one in this particular dermatological disease group. The present study recorded RAU at the time of examination and revealed a prevalence of 2.9%. Since
active lesions of RAU are recurrent and may not exist at the time of examination, patient’s self-reported history has been the main method of defining prevalence of this condition globally. A positive history varied from the subject having had one lesion over his life span to having one lesion in the past two years.

In contrast to many previous studies [53, 66], our data do not support an association between tobacco habits and leukoplakia. The present study showed a low proportion of smokers in the study group with a relatively high proportion of oral leukoplakia. In connection with that, previous studies showed that leukoplakia in non-tobacco users was more likely to undergo malignant transformation than leukoplakia in tobacco users [246, 247]. Knowing that oral leukoplakia, discoid lupus erythematosus and oral lichen planus are potentially malignant disorders [68, 248-250], the present study underscored that the results of Paper I should be considered alarming findings and close clinical follow up is necessary to allow early detection of transformation in these lesions.

In the present study, as well as in other studies, the underlying distribution of risk factors such as tobacco use has a great influence on the total prevalence of OML. In order to capture the true prevalence of the OML in this subset of dermatological patients, repeated multiple clinical examinations of the same population may be necessary, particularly for non-symptomatic conditions which may regress and reappear.

Finally, we can conclude that despite the discussed limitations (Paper 1), our study provides an important contribution to the field of oral health, reflecting a wide spectrum of OML among Sudanese patients in the dermatology clinic.

5.2.2 Impacts of oral mucosal lesions and oral symptoms on mucocutaneous patient’s daily life activities

In Paper II, the number of OML, the number and types of oral symptoms, perceived oral health as well as dental attendance were statistically significantly associated with oral impact on daily performances, OIDP. In addition, patients with vesiculobullous
and ulcerative lesions reported the worst OIDP scores. Notably, both disease groups are chronic or recurrent in nature. The present study accords with that of Tabolli et al. [189] who reported that patients with RAU had mean OHRQoL scores almost twice as high as patients with other OML groups. In a prospective study among patients with various tongue conditions, OHRQoL was reported to be worse in subjects with tongue lesions than in the controls [191]. The study suggested that tongue conditions affect quality of life, but not more so than erosive disorders such as RAU or lichen planus [190, 209]. That might be due to clinical manifestations and the treatment available in the management of such lesions, as reported by Ni Riordain et al. [251, 252].

In the present study, it is important to mention that despite the fact that OIDP was significantly negatively affected in the vesiculobullous and the ulcerative groups, their confidence intervals were wide, indicating less precision in the estimated relationships. This may be attributed to a limited sample size and limited power of the statistical tests. Thus, the present study should be replicated with a larger sample size.

Paper II showed that the prevalence of dental caries experience (DMFT > 0) was 89.9%. This result is in agreement with previous studies done among dental attendees in Sudan. Caries prevalence has been reported to vary between 87.7% and 96% [253, 254]. Dental caries causes dental pain and discomfort, functional limitation, and dissatisfaction with appearance. These symptoms may in turn transform into social problems and low self-esteem [212]. This has been shown in many epidemiological studies using the OIDP inventory across different age groups, where significant associations between dental caries and poorer OHRQoL have been found [255, 256]. Conversely, in the present study, the highly prevalent condition of tooth decay had a small negative impact on OIDP. This might be attributed to the fact that patients learn to cope with commonly occurring symptoms and conditions that become less disabling with recurrence. Also, irrespective to the relatively high DMFT scores in the present study, only 38.4% reported at least one visit to a dental clinic, highlighting a low utilization of dental care. Clinical indicators like DMFT reflect the end point of the disease and provide an indication of treatment needs [257], and they do not reflect the
impact of the disease on daily life and activities. The present study showed that dental attendance pattern was one of the strongest covariates of oral impacts and it increased systematically across the three groups: no OML, one OML, > one OML. That was contrary to the widely recognized positive association between dental attendance and improved oral health, mostly emanating from industrialized countries [258].

Based on the existing literature, pain is the principal symptom that affects OHRQoL [194, 259]. Even with a low prevalence of OML, pain associated with OML was strongly associated with oral impacts, even after controlling for confounding variables. This result was supported by a study done in Sudan by Khalifa et al. [251] which reported that 90% of patients went to the dentist only when they experienced pain [254]. It is likely that the present results may reflect problem-oriented visits, and they may partially explain the association between dental attendance and OHRQoL seen in our study. The current status of the mouth in this study could have influenced other factors that are traditionally recognised as affecting oral health quality of life. Also, we cannot ignore other factors such as attitudes, beliefs, and perceptions which might also have contributed to the present results.

The present data provide additional support to a recent study on chronic oral mucosal conditions; the study found that QoL was negatively affected in the patients when using COMDQ [203-205]. In general, the findings of Paper II support the use of generic OHRQoL measures together with objective clinical measures in oral health assessment in patients with different OML. Furthermore, the results could reflect the efficacy of dental care delivery systems and oral health promotion programs in the country. Great improvement may be expected in such patients, if disease management approaches include the patients’ overall well-being.

5.2.3 Oral pemphigus vulgaris

Acknowledging the findings of Papers I and II, that the vesiculobullous group registered the worst OHRQoL scores of all the oral lesion groups, and that oral PV was the predominant oral lesion in this group, Paper III went deeper, describing many
aspects of Sudanese patients with oral PV attending the main dermatology clinic in Sudan.

In the present study, we found that 95% of pemphigus was PV. Of these cases, 90.4% (19/21) had oral involvement; their mean age was 43.0± 16.5 yr. In 50.0% (9/18) of those who experienced both skin and oral lesions, the symptoms initially manifested themselves in the oral cavity. The oral lesions were manifested as multiple irregular ulcers or erosions that sometimes were covered by a white-yellow slough, mainly located in the buccal and palatal mucosa. These results are in agreement with the international literature and support the paucity of intact bullae or vesicles in the oral cavity [141, 260-262]. The results also showed that pemphigus should be considered when there are multiple persistent oral ulcerations. Furthermore, the severity of these lesions was measured by a modified scoring index, OLAS, which classified lower education, having an outdoor job, living outside Khartoum, being a non-smoker and belonging to a central and Western tribe as having the severest active oral lesions. In the present study, those who reported outdoor jobs (farmer, animal breeder, street seller and builder) and lower education were the low income patients. Health illiteracy and poor general health were known to be associated with these socioeconomic parameters [263, 264]. Living outside Khartoum state might have reflected the geographic distribution of health facilities and personnel, in other words, ease of access to health services [221].

PV is a rare disease that has a distinct geographical distribution and it is associated with multiple factors including genetic, environmental, occupational, behavioral, medical, infection factors and type of food intake [115]. A review study showed that psyche, immunity and skin are commonly related, and a pathogenic link between exhaustive emotional stress and an autoimmune skin disorder can often be visualized [265]. In connection to that, the present study showed the high level of oral PV and OLAS among Western tribes compared with other Sudanese tribes. This result could be in part associated with the war in the south and environmental disasters (drought) in the Western part of Sudan. The higher prevalence of oral PV among outdoor workers
in this study emphasizes the need for sunlight protection measures like sunscreen, cap and hat for outdoor workers.

The results of the present study did not support an association of PV with genetic factors and the tribe’s distribution. This may well be due to the old history of intermarriage among more than fifty ethnic groups and six hundred tribes in Sudan [266]. The small sample size and the absence of a control group preclude any definite assertions in this study. PV has been documented in all races and ethnic groups but with an increased risk in certain ethnic groups. The association with specific HLA class II genes nevertheless suggests a genetic predisposition for the disease [109-111]. It would be interesting to study the genetic profile of Sudanese PV patients.

The presence of a cleft at different levels of the epithelium aids in diagnosing the variants of pemphigus. If the clefts are present directly above basal layer, it is PV, and if it is seen beneath the granular layer, it is pemphigus foliaceus [260]. In the present study, light microscopy revealed the characteristics of PV, suprabasal cleft, acantholysis and Tzanck cells in all oral specimens except one. Also, we managed to detect IgG and C3 deposited in the keratinocytes intercellular spaces in all specimens using IHC on formalin fixed biopsies.

Despite methodological limitations (see Paper III for limitations), the present study provides valuable information on the clinical presentation of oral PV in Sudanese patients, the socio-demographic distribution and how it affected the severity of the oral lesions. The study also highlights the importance of histopathology and the possibility of using IHC on formalin-fixed, paraffin-embedded tissue biopsies to achieve a definite diagnosis when a fresh biopsy and a blood sample are not available.
6. Conclusions

- OML were frequently (57.9%) diagnosed in patients with skin disease and the highest prevalence was among the groups with vesiculobullous reaction pattern and skin tumours.

- Tongue lesions were the most frequently occurring OML group across the various skin diseases. The highest prevalence (33.3%) of tongue lesions was found among psoriasiform reaction pattern.

- OML varied systematically with age, sex, systemic conditions and use of toombak.

- The prevalence of PV was high in the outpatients investigated. More than 90% of patients with pemphigus vulgaris had oral lesions.

- The socio-demographic, clinical and histological picture of oral PV reported in these studies is in good agreement with the literature.

- In the absence of fresh biopsy, IHC on formalin-fixed, paraffin-embedded tissue biopsy can be used to confirm the diagnosis of PV.

- Routine evaluation of the oral cavity during normal dermatological consultation is possible and provides beneficial data for the clinical management of patients with mucocutaneous diseases.

- The Arabic version of the OIDP inventory was able to discriminate between patients with skin disease with and without OML. When the influence of numbers of OML, types and numbers of oral symptoms and specific OML groups were taken into consideration, additional information on OHRQoL was provided. This information can be used in efforts aimed to improve the individual’s quality of life.
7. Future perspectives

- Awareness should be increased among patients that an oral cavity examination extends beyond purely dental issues and can include the detection of disorders that could have more severe and wider consequences for health and wellbeing.

- In Sudan, the standard diagnostic protocol for OML should be supplemented with adjunctive diagnostic devices that could help clinicians to detect early mucosal changes, specifically inflammatory and dysplastic lesions.

- In a country like Sudan, with high population growth and limited resources, population-based studies to estimate prevalence, incidence and causal factors of OML are difficult to conduct. Sample-based surveys are better. When the occurrence of a disease or condition is very rare, there is a high probability that neither method will include a single case. In such cases, to maintain a clinical recording system within the general health care system should be an important goal. This would facilitate retrospective study (e.g. case-control studies) of rare conditions such as PV.

- There is a need for a comparative study focusing on increasing the evidence supporting the validity of the OIDP, other adult OHRQoL instruments and the recently introduced COMDQ among patients with OML, to ensure a good instrument and validate the assessment of the OHRQoL scores between groups within and between cultures.

- We encourage more extensive use of theses OHRQoL instruments for cases of OML at outpatient clinics in oral medicine and dermatology clinics.

- Treatment of patients with OML should extend beyond a merely biological focus to social and psychological aspects with a view to producing better quality of life for the patients.

- An interdisciplinary approach in the management of such patients is imperative.
• The list of risk factors that trigger pemphigus has grown in the recent years, therefore a comprehensive study investigating PV and different risk factors in Sudanese patients is recommended.
8. References


220. **Health System Profile Sudan**
   

221. **Annual Health Statistical Report-2010**
   


223. **Annual Health Statistical Report-2007**
   


225. **Sudan, Country statistics**
   
   [http://apps.who.int/ghodata/?theme=country]

226. **Background Note: Sudan**
   
   [http://www.state.gov/r/pa/ei/bgn/5424.htm]


9. Appendix

9.1 Appendix

**Adult OIDP inventory-English version**

**Personal information**
- **Date**: ……………………
- **Code**: ………………………
- **Name**: ………………………
- **Age**: ……………………

**Section 1:**

1. **Gender**
   - 1. F
   - 2. M

2. **Tribe**
   - 1. Northern
   - 2. Southern
   - 3. Western
   - 4. Eastern
   - 5. Central

3. **Marital status**
   - 1. Unmarried
   - 2. Married
   - 3. Divorced
   - 4. Engaged
   - 5. University
   - 6. Widows
   - 7. Other

4. **Level of education**
   - 1. Illiterate
   - 2. Primary school
   - 3. Secondary school
   - 4. University
   - 5. Higher studies

5. **Occupation**
   - 1. Professional
   - 2. Office labour
   - 3. Skilled labour
   - 4. Student
   - 5. Unemployed
   - 6. Farmer
   - 7. Animal breeder
   - 8. Others (specify)

6. **Residence during last 5 years**
   - 1. Khartoum state
   - 2. Northern state
   - 3. Southern state
   - 4. Eastern state
   - 5. Western state
   - 6. Central state
   - 7. Out of Sudan
   - 8. Others(specify)

7. **Family medical History**
   - 1. Yes, specify
   - 2. No

8. **Current Treatment**
   - 1. No
   - 2. Yes, Specify

9. **Drug history**
   - 1. Known allergic to certain drug
   - 2. Chronic use for certain drug

10. **Medical History**

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<tr>
<th>Condition</th>
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<tr>
<td>Cancer</td>
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</table>

**Section 2:**

During the latest 6 months, have you had problems with your mouth and/or teeth caused you any difficulties with the following situations?

1. **Eating and chewing food**
   - Never
   - Less than once a month
   - Once or twice a month
   - Once or twice a week
   - Every, or nearly every day

2. **Speaking and pronouncing clearly**
   - Never
   - Less than once a month
   - Once or twice a month
   - Once or twice a week
   - Every, or nearly every day

2. **Cleaning your teeth**
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

### 2.4 Sleeping and relaxing
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

### 2.5 Maintaining usual emotional state
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

### 2.6 Carrying out major work?
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

### 2.7 Enjoying contact with people
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

### 2.8 Smiling and showing teeth
1. Never
2. Less than once a month
3. Once or twice a month
4. Once or twice a week
5. Every, or nearly every day

Section 3:
Some questions about how you consider your overall health status

#### 1.1 How do you evaluate your general health status?
1. Very bad
2. Bad
3. Neither good nor bad
4. Good
5. Very good

#### 1.2 How do you consider the present condition of your mouth and teeth?
1. Very bad
2. Bad
3. Neither good nor bad
4. Good
5. Very good

#### 1.3 Are you satisfied with the appearance of your teeth?
1. Strongly disagree
2. Disagree
3. Neither agree nor disagree
4. Agree
5. Strongly agree

Section 4: During the previous 6 month have you experienced?

#### 4.1 Dental pain/toothache?
1. Yes
2. No
3. I do not know

#### 4.2 Abscessed tooth?
1. Yes
2. No
3. I do not know

#### 4.3 Dry mouth?
1. Yes
2. No
3. I do not know

#### 4.4 Infected sore gums
1. Yes
2. No
3. I do not know

#### 4.5 Bleeding gums?
1. Yes
2. No
3. I do not know

#### 4.6 Tooth decay
1. Yes
2. No
3. I do not know

#### 4.7 Broken tooth
1. Yes
2. No
3. I do not know

Section 5: Some questions about your life style and Oral health related behaviours

#### a. Have you ever attended a dentist (dental therapist) for treatment?
1. Yes
2. No
3. Don’t know

#### b. Do you have a dentist (dental therapist) to go to if you need one?
1. Yes
2. No
3. Don’t know

#### c. Think back on the previous 2 years – how many times have you attended a dentist?
1. Once
2. Twice
3. More than twice
4. Never

#### d. How often do you brush your teeth?
1. Several times a day
2. Daily
3. Seldom
4. Never

#### e. Alcohol-drinking habits
1. Every day
2. Several times a week
3. Some times
4. Never
5. Former drinker

#### f. Tobbaco use
1. Every day
2. Several times a week
3. Sometimes
4. Never
5. Former use
<table>
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<tr>
<th></th>
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<th></th>
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<tr>
<td>1</td>
<td>Smoke every day</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Some times</td>
<td>4</td>
</tr>
</tbody>
</table>
9.2 Appendix

Adult OIDP inventory - Arabic version

Patient Personal Data:

Code: .................................. Date: ..................................
Name: .................................... Age: ..............................

القسم الأول:

أ/ خلال الـ 6 أشهر الماضية كم من المرات عانيت من مشاكل تتعلق بالقدم والأسنان مما نتج عنه صعوبة في الأكل ومضغ الطعام؟
1/ ولا مرة
2/ أقل من مرة في الشهر
3/ مرة أو مرتان في الشهر
4/ مرة أو مرتان في الأسبوع
5/ تقريبا أو كل يوم

ب/ خلال الـ 6 أشهر الماضية كم من المرات عانيت من مشاكل تتعلق بالقدم والأسنان مما نتج عنه صعوبة في الكلام؟
1/ ولا مرة
2/ أقل من مرة في الشهر
3/ مرة أو مرتان في الشهر
4/ مرة أو مرتان في الأسبوع
5/ تقريبا أو كل يوم

ت/ خلال الـ 6 أشهر الماضية كم من المرات عانيت من مشاكل تتعلق بالقدم والأسنان مما نتج عنه صعوبة في النوم والاسترخاء؟
1/ ولا مرة
2/ أقل من مرة في الشهر
3/ مرة أو مرتان في الشهر
4/ مرة أو مرتان في الأسبوع
5/ تقريبا أو كل يوم

ث/ خلال الـ 6 أشهر الماضية كم من مرات عانيت من مشاكل تتعلق بالقدم والأسنان مما نتج عنه صعوبة في إظهار الأسنان؟
1/ ولا مرة
2/ أقل من مرة في الشهر
3/ مرة أو مرتان في الشهر
4/ مرة أو مرتان في الأسبوع
5/ تقريبا أو كل يوم

د/ خلال الـ 6 أشهر الماضية كم من مرات عانيت من مشاكل تتعلق بالقدم والأسنان مما نتج عنه صعوبة في الرقص أو الخجل من إظهار الأسنان؟
1/ ولا مرة
2/ أقل من مرة في الشهر
3/ مرة أو مرتان في الشهر
4/ مرة أو مرتان في الأسبوع
5/ تقريبا أو كل يوم

القسم الثاني:

أ/ ما هو تقييمك لصحتك العامة؟
1/ سيئ جدا
2/ سيئ
3/ لا إجابة
4/ جيد
5/ جيد جدا
قسم الثالث

أ/ خلال ال 6 أشهر الماضية هل كان لديك الام في الأسنان؟

1/ نعم
2/ لا
3/ لا أدرى

ب/ خلال ال 6 أشهر الماضية هل كان لديك خراج في الأسنان؟

1/ نعم
2/ لا
3/ لا أدرى
4/ لا إجابة

ت/ خلال ال 6 أشهر الماضية هل كان لديك فافط في الفم؟

1/ نعم
2/ لا
3/ لا أدرى

ث/ خلال ال 6 أشهر الماضية هل كان لديك تسوس في اللثة؟

1/ نعم
2/ لا
3/ لا أدرى

د/ خلال ال 6 أشهر الماضية هل كان لديك نزيف في اللثة؟

1/ نعم
2/ لا
3/ لا أدرى

إ/ خلال ال 6 أشهر الماضية هل كان لديك اسنان متسوسة؟

1/ نعم
2/ لا
3/ لا أدرى
4/ لا إجابة

ج/ خلال ال 6 أشهر الماضية هل كسرت احدى اسنانك؟

1/ نعم
2/ لا
3/ لا أدرى

القسم الرابع

أ/ هل زهبت إلى عيادة أسنان في حياتك لتلقى العلاج؟

1/ نعم
2/ لا
3/ لا أدرى

ب/ خلال العامين الماضيين كم مرة ذهبت إلى عيادة أسنان لتلقى علاج؟

1/ مرة واحدة
2/ مرتان
3/ أكثر من مرتين
4/ لا أذهب

ت/ هل لديك طبيب أسنان تذهب إليه عند الحاجة؟

1/ نعم
2/ لا
3/ لا أدرى

ث/ كم مرة تنظف أسنانك بفرشاة الأسنان؟

1/ عدة مرات في اليوم
2/ مره واحدة في اليوم
3/ نادرا
4/ ولا مره

د/ إذا كنت من المدخنين – ما هو معدل التدخين عندك؟

1/ أكثر من مرتين
2/ مرتان
3/ مرة واحدة
4/ لا أدخن
5/ لا أدخن إطلاقا

إ/ إذا كنت تعاطي الكحول – ما هو معدل تعاطي الكحول عندك؟

1/ يوميا
2/ عدة مرات في الأسبوع
3/ أحيانا
4/ لا أتعاطي الكحول
5/ لا أتعاطي في الماضي

ج/ إذا كنت من مستخدمي التمباك – ما هو معدل استخدامك؟

1/ يوميا
2/ عدة مرات في الأسبوع
3/ أحيانا
4/ لا أسخدم التمباك
5/ لا أسخدم في الماضي
9.3 Appendix

Skin examination sheet:

Patient Personal Data:

Code: ……………………………
Date ……………………………..
Name ……………………………
Age ……………………………….

Section 1

1. Chief complaints (C/C)
   1. Localised pruritis
   2. Generalised pruritis
   3. Eruption
   4. Dryness
   5. Hypopigmentation
   6. Swelling
   7. Numbness
   8. Hyperpigmentation
   9. Malaise
   10. Others (specify)

1.1 Duration of C/c:
   1. Days
   2. Weeks
   3. Months
   4. Years

1.2 The current history of C/C:
   When
   1. Less than 4 days
   2. More than 4 days
   3. More than a week

1.3 Where
   1. Face
   2. Neck
   3. Chest
   4. Trunk
   5. Genital organs
   6. Upper limbs
   7. Lower limbs
   8. Back
   9. Scalp
   10. Buttocks
   11. Generalized

1.4 Onset/ How
   1. Abrupt
   2. Insidious
   3. Sudden
   4. Rapid
   5. Gradual
   6. Indolent

1.5 Course
   1. Remittent (fluctuant, relapsing)
   2. Progressive

3. Stationary (static)
4. Regressive

1.6 Aggravating factors
   1. Sun exposure
   2. Smoking
   3. Alcohol
   4. Spices
   5. Stress
   6. No aggravating factors
   7. Others (specify): ………………………………

1.7 Alleviating factors
   1. Sun exposure
   2. Smoking
   3. Alcohol
   4. Spices
   5. Stress
   6. No alleviating factors
   7. Others (specify):

1.8 Associations
   1. Fever
   2. Loss of weight
   3. Loss of appetite
   4. Diarrhoea
   5. Polyuria
   6. Night cough
   7. Sweating
   8. No association
   9. Others (specify)

1.9 First lesions
   Where
   1. Skin only
   2. Oral cavity only
   3. Skin first and then oral cavity
   4. Oral cavity first and then skin
   5. Skin and oral cavity simultaneously

1.10 Past history of the current condition
   1. Yes
   2. No

2. 1.11 Family history of similar condition
   1. Yes
   2. No

1.12 Treatment
   1. Not under treatment
   2. Under treatment (specify)

1.13 Sexual history
   1. Urethral discharge
   2. Genital ulcers
   3. Multiple sexual relationships
   4. Homosexuality
   5. Bisexuality
   6. No sexual history

Section 2
2.1 General examinations

A. General condition
1. Ill
2. Febrile
3. Pale
4. Cyanotic
5. Icteric
6. Emaciated
7. Wasted
8. Dehydrated
9. Looks well

B. Vital sign measures
1. Temperature
2. Pulse
3. Blood Pressure

C. Specific organ examination Systemic (examination)
1. Normal condition
2. Abnormal condition, specify
3. Head
4. Neck
5. Chest
6. CVS
7. LL (oedema, varicose veins)
8. LN
9. CN

2.2 Distribution of cutaneous lesion

A. Localized
1. Single lesion
2. Cluster
3. To specific part (Systematized)
4. To stereotypical part

B. Widespread
1. Scattered to individual lesion
2. Unilateral
3. Bilateral
4. Symmetrical
5. Asymmetrical
6. Along a line of Cleavage; Pityriasis rose
7. Diffuse involvement
8. Universal

2.3 Configuration of cutaneous lesions

A. Linear
1. Confluent
2. Separated in file

B. Arciform
1. Annular
2. Polycyclic
3. Serpentine

C. Circular
1. Guttate
2. Nummular

D. Grouped
1. Herpitiiform
2. Zosteriform
3. Corymbiform
4. Agminated
5. Moniliform

2.4 Morphology of individual lesions (Fundamental cutaneous lesions) (words)

1. Macules
2. Papules
3. Nodules
4. Vesicles
5. Bullae
6. Pustules
7. Patches
8. Plaques
9. Crust
10. Keratosis
11. Scale crust
12. Eschars
13. Erosions
14. Ulcers
15. Fissures
16. Atrophies
17. Telangiectasia
18. Burrows

2.5 Lesion colour
1. White
2. Yellow
3. Brown
4. Red
5. Violet
6. Blue
7. Black
8. Others

2.6 Palpation of cutaneous lesion
1. Soft
2. Firm
3. Hard
4. Fluctuant
5. Compressible
6. Doughy
7. Others.

2.7 Provisional diagnosis

2.8 Confirmatory investigations
1. Skin biopsy
2. Skin scraping for fungal infection
3. Nail clip for fungal infection
4. Skin smear for Leishmania Donovani bodies (L.D.bodies)
5. Skin snip for Onecocera Volvulous (O.V.)
6. Skin swab for culture and sensitivity (C&S)
7. Skin swab for Alcoholic Acid Fast Bacilli (A.A.F.B.)
8. Slit skin smear of Mycobacterium Librue

2.9 Final diagnosis

................
9.4 Appendix

Oral examination sheet:

**Patient Personal Data:**

- Code: --------------------------------------
- Date: ---------------------------------------
- Name: -------------------------------------
- Age: ----------------------------------------

**Section 1**

**A. Patient’s chief complaint (C/C)**

1. Burning sensation
2. Dryness
3. Pain
4. Swelling
5. Numbness
6. Hyperpigmentation
7. Difficult eating/swallowing
8. No complain
9. Bleeding
10. Bad taste or smell
11. Swelling or tenderness of adjacent lymph nodes
12. Other (specify) : …………………………………………..

**B. Duration of C/C:**

1. Days
2. Weeks
3. Months
4. Years

**C. History of C/C:**

1. Trauma
2. Habits
3. medicine
4. food
5. Toothpaste
6. Denture
7. Toothache
8. No reason
9. Others(specify)-------------------------------------

**D. Onset/ How**

1. Insidious
2. Sudden
3. Rapid
4. Gradual
5. Indolent

**E. Course**

1. Remittent (fluctuant, relapsing)
2. Progressive
3. Stationary (static)
4. Regressive

**F. Aggravating factors**

1. Sun exposure
2. Smoking
3. Alcohol
4. Spices
5. Stress
6. No aggravating factors
7. Others (specify) --------------------------------------

**G. Alleviating factors**

1. Sun exposure
2. Smoking
3. Alcohol
4. Spices
5. Stress
6. No Alleviating factors
7. Others (specify) --------------------------------------

**H. Change in physical character**

1. Lump to ulcer
2. Vesicle to ulcer
3. No change
4. Others(specify)-------------------------------------

**5. K. Current treatment for the current lesion**

1. No
2. Yes specify---------------------------------

**Section 2**

**2.1 Extra Oral Examination**

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<td>Lower lip</td>
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<tr>
<td>Perioral area</td>
<td>3</td>
</tr>
<tr>
<td>Commissures</td>
<td>4</td>
</tr>
<tr>
<td>Vermilion boarder</td>
<td>5</td>
</tr>
<tr>
<td>LN (head &amp; neck)</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code</th>
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<td>Atrophy</td>
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<td>Hypopimentation</td>
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</table>

**Section 3**

**3.1 Intra Oral Examination Oral mucosa**

**A. Number of different types of lesions**

1. Single
2. Two
3. Multiple
4. No lesion detected

**B. Size of the lesion**

1. Less than 0.5 cm
2. More than 0.5 cm
3. More than 1.0 cm

**C. Surface of the lesion**

1. Smooth
2. Irregular
3. Covered by yellow fibrinous membrane
4. Lobulated
5. Filmy/milky surface
6. Verrocous growth
7. Granular
8. Atrophic

D. Ulcer base
1. Smooth
2. Full of granulation tissue
3. Fungated
4. Covered with slough membrane or scab

E. Consistency/ texture of the lesion - palpation
1. Soft
2. Firm
3. Hard
4. Indurated (hard or firm)
5. Fluctuation
6. Spongy

F. Mobility of the lesion
1. Fixed
2. Movable
3. Matted

G. Presence of pulsation
1. Yes
2. No

H. Margin of the lesion
1. Flat
2. Rolled
3. Raised
4. Everted
5. Irregular (ill-defined margin)
6. Well demarcated

3.2 Describe pain
1. No pain
2. Pain
3. Mild
4. Moderate
5. Severe

3.3 Past history of the current lesions
1. Yes
2. No

3.4 Family history of similar condition
1. Yes
2. No

3.5 History of RAU if present
   Times of recurrence
1. Once during the last year
2. Twice during the last year
3. More than two during the last year
4. First time

3.6 Condition and Location

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<td>Leukoplakia</td>
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<td>Lips</td>
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<td>Sulci</td>
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<td>Buccal mucosa</td>
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<tr>
<td>Floor of the mouth</td>
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</tr>
<tr>
<td>Tongue</td>
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</tr>
<tr>
<td>Soft palate</td>
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<tr>
<td>Hard palate</td>
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</tr>
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<td>Alveolar ridge/ gingiva</td>
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<tr>
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</table>

3.7 Biopsy
   Incision
   1. Excision
   2. Punch
   3. No biopsy taken

   a. Differential Diagnosis:
      ------------------------------------------
      ------------------

   b. Investigations
   1. Histopathology
   2. Haematology
   3. Microbiology
   4. Other

   c. Results: ------------------------------------------
      ------------------
      -----

   d. Final Diagnosis: ------------------------------------------
      ------------------
Section 4
Dentition status registration: (DMFT):

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Criteria and codes for dentition registration:

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<td>Missing any other reason</td>
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<td>Fissure sealant</td>
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<td>Bridge, abutment, crown</td>
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<td>Un-erupted crown</td>
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<td>Trauma/fracture</td>
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9.5 Appendix

**Oral mucosal lesions encountered during the study period**

<table>
<thead>
<tr>
<th>Coated</th>
<th>Geographic</th>
<th>Fissured</th>
<th>Atrophy of papillae</th>
<th>Geographic+ fissured</th>
<th>Tongue tie</th>
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<tr>
<td>Snuff dipper lesion</td>
<td>Frictional keratosis</td>
<td>Leukoplakia code</td>
<td>Nicotinic stomatitis</td>
<td>Lupus erythematosus</td>
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<td>Unspecified nicotinic stomatitis</td>
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<td>Erosion</td>
<td>Erosion</td>
<td>Hemangioma</td>
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<td>Pemphigus vulgaris</td>
<td>Chickenpox</td>
<td>Bullous pemphigoid</td>
<td>Herpes labialis</td>
<td>Vesic.bullous not verified</td>
<td></td>
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</tbody>
</table>
RAS  Drug reaction  Stevens-johnson syndrome  Erythema multiform

Oral melanotic macules  Oral melanotic macules  Gingival tattoo  Fibroepithelial polyp  Denture induced fibrous hyperplasia

Erythematous candidiasis  Median rhomboid glossitis  Pseudomembranous candidiasis  Angular cheilitis  Hyperplastic candidiasis

Soft tissue like lesion  Palatal tori  Exostosis  Perioral dermatitis  Perioral wart

Hypopigmented lip  Cheilitis glandularis  Unspecified cheilitis  Papillary hyperplasia  Focal epithelial hyperplasia

Mucocele  Kaposi sarcoma
10. Original papers I -III
Oral mucosal lesions in skin diseased patients attending a dermatologic clinic: a cross-sectional study in Sudan

Nada M Suliman¹, Anne N Åstrøm², Raouf W Ali³, Hussein Salman⁴ and Anne C Johannessen¹,5*

Abstract

Background: So far there have been no studies focusing on the prevalence of a wide spectrum of oral mucosal lesions (OML) in patients with dermatologic diseases. This is noteworthy as skin lesions are strongly associated with oral lesions and could easily be neglected by dentists. This study aimed to estimate the frequency and socio-behavioural correlates of OML in skin diseased patients attending outpatient’s facility of Khartoum Teaching Hospital - Dermatology Clinic, Sudan.

Methods: A cross-sectional hospital-based study was conducted in Khartoum from October 2008 to January 2009. A total of 588 patients (mean age 37.2 ± 16 years, 50.3% females) completed an oral examination and a personal interview of which 544 patients (mean age 37.1 ± 15.9 years, 50% females) with confirmed skin disease diagnosis were included for further analyses. OML were recorded using the World Health Organization criteria (WHO). Biopsy and smear were used as adjuvant techniques for confirmation. Data were analysed using the Statistical Package for Social Science (Version 15.0.1). Cross tabulation and Chi-square with Fisher’s exact test were used.

Results: A total of 438 OML were registered in 315 (57.9%, males: 54.6% versus females: 45.6%, p < 0.05) skin diseased patients. Thus, a certain number of patients had more than one type of OML. Tongue lesions were the most frequently diagnosed OML (23.3%), followed in descending order by white lesions (19.1%), red and blue lesions (11%) and vesiculobullous diseases (6%). OML in various skin diseases were; vesiculobullous reaction pattern (72.2%), lichenoid reaction pattern (60.5%), infectious lesions (56.5%), psoriasiform reaction pattern (56.7%), and spongiotic reaction pattern (46.8%). Presence of OML in skin diseased patients was most frequent in older age groups (62.4% older versus 52.7% younger, p < 0.05), in males (63.2% males versus 52.6% females, p < 0.05), patients with a systemic disease (65.2% with systemic versus 51.9% without systemic disease, p < 0.05) and among current users of smokeless tobacco (toombak) (77% current use versus 54.8% no use, p < 0.00).

Conclusions: OML were frequently diagnosed in skin diseased patients and varied systematically with age, gender, systemic condition and use of toombak. The high prevalence of OML emphasizes the importance of routine examination of oral mucosa in a dermatology clinic.

Background

Epidemiological studies of oral mucosal lesions (OML) are rare globally in comparison with studies on caries and periodontal diseases [1]. Whilst caries and periodontal diseases constitute the most prevalent oral diseases worldwide, cancrum oris, oral manifestations of HIV/AIDS, and oral cancer constitute the main burden of oral diseases in deprived communities in sub Saharan Africa [2]. As the pattern of oral diseases vary across countries, site specific epidemiological studies are needed to address the most commonly occurring oral diseases in order to plan for oral health care service [1,3].

To estimate the prevalence, incidence, distribution and causal factors of OML, studies from the general population are needed. However, population based studies are difficult to carry out because they are expensive and time consuming. The most extensive surveys on OML have been reported from Sweden, America, Malaysia and India.

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Absence of use of standardized methodological design in epidemiological studies of OML has shown substantial disparity in the prevalence of these lesions across different settings worldwide. In general, previous studies have shown that OML tend to increase with age and being a male, and also with lifestyle patterns such as tobacco and alcohol consumption [6,12,17].

In oral medicine, dermatologic diseases have got special attention as OML may be the primary clinical feature or the only sign of various mucocutaneous diseases [18-20]. Focusing on patients referred to a dermatologic clinic, Ramirez-Amador et al [21] reported a prevalence of 35% OML in subjects affected with mucocutaneous conditions. Pemphigus vulgaris, lichen planus, candidiasis, and recurrent aphthous ulcers were the most frequently diagnosed conditions [21]. Yet, there has been no studies focusing on the prevalence of a wide spectrum of different types of OML in patients with dermatologic diseases. This is noteworthy as a certain amount of skin lesions are strongly associated with oral lesions and could be neglected by dentists due to lack of information and/or improper diagnosis [22]. Dentists are often the first to be consulted by patients who develop acute oro-facial pain. Therefore, improving the knowledge about the frequency and diversity of OML at the dermatology clinic will strengthen and enhance interdisciplinary and multispectral approaches as opposed to a single sector approach in the management of such patients. Moreover, OML in skin diseases deserve special attention, considering that some are life-threatening, while others have great impact on individuals and society in terms of pain, discomfort and social and functional limitations [1]. In the Sudan, studies on OML have focused on toombak (Sudanese smokeless tobacco)-associated lesions since several clinical and epidemiological studies have identified toombak use as a possible risk factor for oral cancer [23,24].

**Purpose**
The purpose of this study was to estimate the frequency, diversity and socio-behavioural correlates of different types of OML in adult patients with dermatological diseases attending outpatient’s facility of Khartoum Teaching Hospital (KTH) - Dermatology Clinic, Sudan.

**Methods**
**Sampling procedure**
A cross sectional hospital-based study was carried out focusing on patients aged 18 years and above with skin lesions, attending an outpatient dermatologic clinic at KTH from October 2008 to January 2009. KTH is the largest national hospital in Sudan. It is an open public and referral hospital receiving patients from all states of the country. A minimum sample size of 500 patients was calculated based on an assumed prevalence of OML in skin diseased patients of 5%, a confidence interval of 95%, and an absolute precision of 0.02. All patients (n = 4235) attending the outpatient facility during the survey period were invited to participate in the study. The patients were informed in detail about the study procedure and that they could decline at any time without negative consequences, after having given consent.

A total of 1540 subjects (36.4%) accepted verbally to participate in the study. Fear of taking biopsy for asymptomatic lesions and time consuming examinations (oral examination, interview, and biopsy when needed) were the main reasons for not volunteering to participate. Some refusals did not give reason for non-participation. Among those who initially accepted to participate, 544 (544/1540, 35.3%) patients were included in the study. Reasons for none consenting were patients’ disappearance and limited resources. Confidentiality of the patients was maintained. The participants were informed about their oral conditions, and health education was provided. Those who needed dental services were referred to the University of Science and Technology (UST), Faculty of Dentistry, for further investigation and management. Participation was voluntary. Written informed consent or finger print for participation and publication of the study was obtained from patients or their parents/guardians. The research conformed to the Helsinki Declaration and ethical clearance, and approval letters were obtained by the participating institutions’ committees (UST and KTH, Department of Dermatology, in Sudan). In Norway, the ethical approval was obtained from the Regional Committee for Medical Ethics in Research.

**Interview**
A face-to-face interview was conducted by two trained dentists. The structured interview schedule contained questions regarding socio-demographics (gender, age, education, occupation and place of residence during the last 5 years), health and oral health related characteristics and lifestyle (smoking, use of toombak or alcohol). The interview schedule was constructed in English and then translated and used in Arabic. Forward and backward translations were done by two independent Sudanese professional translators in Arabic and English language. Oral health related behaviours were assessed in terms of use of toombak, alcohol and smoking. Use of alcohol and use of toombak was assessed using a 5-point scale: (1) Every day; (2) Several times a week; (3) Sometimes; (4) Never; (5) Former use. Two dummy variables were constructed yielding the categories 0 = never (including the original categories 4), 1 = yes (including the original
categories 1, 2, 3 and 5). Smoking habit was assessed using a 4-points scale: (1) Every day; (2) Sometimes; (3) Former use; (4) Never. Those scales were dichotomized into 1 = smoke (including the original categories 1, 2 and 3), 0 = never smoke (including the original categories 4).

**Skin examination**

An expert dermatologist (HS) evaluated the patient’s dermatological disease through information obtained in a structured interview conducted in the outpatient department of the dermatology clinic. Elements evaluated during skin examination were chief complains, and duration and history of chief complains. Past history and family history were also recorded.

**Clinical oral examination**

Systematic comprehensive extra-oral and intra-oral clinical examinations based on visual inspection and palpation, following the World Health Organization (WHO) criteria for field surveys [25] were carried out by a dentist (NMS) who received a standard training in diagnosis of OML before the data collection (The Gade Institute, Section for Pathology, and Department of Clinical Dentistry—Section for Oral Surgery and Oral Medicine, University of Bergen, Norway). Oral examination was performed with the subject lying on a medical couch in the outpatient’s section of the Department of Dermatology, KTH. All instruments used for oral examination and biopsy were obtained from UST. A head light and an artificial light, mouth mirrors, spatulas, and sterile gauze were used. Occasionally, a cotton swab was used to remove debris to test whether a white lesion could be wiped off. Dentures were removed prior to examination. In those cases requiring further examination; diascopy, smears for *Candida albicans*, punch and incision biopsies were performed to establish precise accurate diagnosis. In addition, selected sections were stained for examination of *Candida albicans* or melanin. Final diagnoses of all lesions were confirmed by an expert oral pathologist (ACJ). Skin lesions and OML encountered during the survey were photographed using a digital camera (Canon EOS 400D).

Clinical parameters were recorded using a structured questionnaire modified from the WHO OML form assessment [25,26]. Parameters which were recorded were: chief complains, disease history, clinical features of the lesion, anatomical location, size, colour, past history, medications used, and associated etiological factors. Self-reported condition of the oral mucosa was also ascertained by asking the patients about dryness of mouth, ulceration, pain, difficulties in swallowing, and burning sensation. The clinical diagnoses of OML were sorted into 14 disease groups, and the total number of types of lesions within each disease group was assessed. In addition, the total number of patients who were diagnosed with any lesion in each separate disease group was counted. Individual patient could have more than one type of OML diagnosed. Consequently, the number of OML would exceed the number of patients.

**Diagnostic criteria for oral mucosal lesions**

An OML was defined as any abnormal change or any swelling on the oral mucosal surface. Diagnostic criteria for OML were based on Axell criteria and those defined in previous studies and reviews [5,25,27,28]. Thus, median rhomboid glossitis was defined as asymptomatic, smooth to lobulated well demarcated erythematous zone, surrounded by a sharp furrow that affects midline of posterior dorsal tongue. Atrophy of tongue papillae not compatible with the criteria set for median rhomboid glossitis, has been registered as atrophy of tongue papillae. Vitiligo was defined as depigmented macules and patches that have relatively distinct and possibly hyperpigmented margins present in the lips. The lesion should associate with diagnosed vitiligo elsewhere in the skin. Lichenoid lesions were defined as lesions that have in common basal cell damage, have a lichen planus like aspect, but that lack one or more characteristic clinical aspects [29]. Erythema was defined as redness of the mucosa, caused by hyperemia of the mucosal capillaries. The lesion should disappear on finger pressure (blanching).

In addition to strictly intraoral lesions, angular cheilitis and perioral dermatitis were also recorded. Linea alba, cheek biting, leukoedema, lingual varicose, Fordyce’s granules, and excessive melanin racial pigmentation were excluded from the study.

**Statistical analysis**

Data were analyzed using the Statistical Packages for Social Sciences (SPSS, version 15.0). The level of statistical significance was set at 5%. Cross tabulation and Chi-square with Fisher’s exact test were used to test the statistical significance of the relationships between skin disease groups and types OML on the one hand side and socio-behavioural variables on the other.

**Results**

**Sample profile**

A total of 544 patients with a skin disease diagnosis participated in the present study. The mean age was 37.1 ± 15.9 years (range 18-85), 50% were females and 77% were permanent residents of Khartoum during the previous 5 years. Males were more frequently employed than females (72.6% versus 27.4%, \( p < 0.001 \)), whereas use of smoking, toombak or alcohol was more reported in males than females (\( p < 0.05 \)). Totals of 17.7%, 12.7% and 4.3% confirmed former or current smoking, use of toombak and alcohol use, respectively (Table 1).
Skin diseases profile

Ninety-four different types of skin lesions, grouped into 22 categories of skin diseases, were diagnosed. The categories of skin diseases that affected less than 10 patients (13 of the 22 categories) were grouped together and labelled “others”. Spongiotic reaction pattern was the most frequently diagnosed dermatological disease group (126/544, 23.2%), followed in descending order by skin infectious diseases (115/544, 21.1%, i.e. fungal infections 9.6%, viral infection 6.8%, bacterial infection 2.9%, and protozoal infection 1.8%), vesiculobullous reaction pattern (54/544, 9.9%), and disorders of cutaneous appendages (48/544, 8.8%). The least frequently diagnosed group was tumours (12/544, 2.2%) (Figure 1). Disorder of pigmentation was more common in females than in males (78% versus 22%, p < 0.001). Vesiculobullous reaction pattern and disorders of cutaneous appendages were most common in older (32.7% versus 67.3%) and younger (85.4% versus 14.6%) patients, respectively (p < 0.05).

Oral mucosal lesions profile

In total, 315 of the 544 patients included in the study had at least one clinically recognized type of OML (57.9%). A certain amount of the patients had more than one type of OML, thus the total number of OML recorded in the 315 patients was 438. Of those affected, 202 (64.1%) had one type of OML, 78 (24.8%) had two types of OML, and 35 (11.1%) had three or more types of OML. A total of 51 different clinical diagnoses were recorded. For each patient, one type of OML was only recorded once, although in some patients the OML could be manifested at several locations. Only 15.9% (n = 50) of the patients agreed to undergo punch biopsy confirmation. Absence of epithelial dysplasia was confirmed in all biopsies taken from lesions such as oral leukoplakia, frictional lesion, and snuff dipper lesions.

The age of patients affected by OML ranged from 18 to 81 years, with an average of 38.6 years (±16.5). As shown in Table 2, tongue lesions were the most frequently diagnosed OML (23.3%) followed in descending order by white lesions (19.1%), red and blue lesions (11%) and vesiculobullous diseases (6%). The least frequently diagnosed OML group was malignant tumours (0.2%). White lesions (42.2% versus 57.8%) and the red and blue lesions (37.3% versus 62.7%) occurred most frequently in older patients (p < 0.05). Ulcerative conditions were most frequently diagnosed in males (18% versus 6%, p < 0.05). Coated tongue (48.0%) and tongue tie (3.1%) were the most frequently occurring OML within tongue lesions, whereas snuff dipper lesions/toombak-associated lesions...
(28.8%), erythema (48.3%), and pemphigus vulgaris (46.9%) were the most frequently occurring diagnoses in white lesions, red and blue lesions and vesiculobullous diseases, respectively. A total of 0.2% of the patients investigated presented with Kaposi’s sarcoma, the only lesion in the group of malignant tumours.

Table 3 depicts the frequency distribution of OML groups within each skin disease group investigated. OML occurred most frequently in the group of skin vesiculobullous reaction pattern (72.2%), followed in descending order by tumours (66.7%), and lichenoid reaction pattern (60.5%). OML occurred least frequently in the skin disease group of spongiotic reaction pattern (46.8%).

Tongue lesions were the most frequently occurring OML group (23.3%) followed by white lesions (19%), red and blue lesions (11%) and vesiculobullous diseases (6%). White lesions and red and blue lesions varied systematically with age, being most frequent in older persons, whereas ulcerative conditions were most common in males. Coated tongue, snuff dippers lesion, erythema and pemphigus vulgaris

Discussion

Frequency and diversity of oral mucosal lesions

To our knowledge this study is the first to assess the frequency and diversity of OML in dermatologic patients, a selected group of the Sudanese adult population. The study group comprised patients with a wide range of dermatological diseases, yielding small numbers in each group, thus limiting the probability for stratified analyses. The most frequently occurring groups of dermatological diseases were spongiotic reaction pattern, infectious diseases, and vesiculobullous diseases. This accords with the results of a recent survey by the International Foundation of Dermatology, reporting that infectious disease, dermatitis, and HIV-related skin disease are the main skin dermatological conditions at the community level worldwide [30].

According to the present results, about 58% of the subjects investigated suffered from at least one type of OML, and the occurrence of any OML varied across groups of dermatological diseases from 46.8% in spongiotic to 72.2% in vesiculobullous reaction patterns. Tongue lesions were the most frequently occurring OML group (23.3%) followed by white lesions (19%), red and blue lesions (11%) and vesiculobullous diseases (6%). White lesions and red and blue lesions varied systematically with age, being most frequent in older persons, whereas ulcerative conditions were most common in males. Coated tongue, snuff dippers lesion, erythema and pemphigus vulgaris
Table 2: Prevalence of oral mucosal lesions in the total group of skin diseased patients (n = 544), in the group of skin diseased patients with OML and within the 14 most frequently occurring OML groups

<table>
<thead>
<tr>
<th>Oral mucosal lesions</th>
<th>Proportion with a specific lesion in the total group of patients (n = 544)</th>
<th>Proportion with a specific lesion in the total group of patients with any OML (n = 315)</th>
<th>Proportion with specific lesion within 14 OML groups</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tongue lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coated tongue</td>
<td>61 (11.2) %</td>
<td>19.4 %</td>
<td>48.0 %</td>
<td></td>
</tr>
<tr>
<td>Fissured tongue</td>
<td>26 (4.8)</td>
<td>8.3 %</td>
<td>20.5 %</td>
<td></td>
</tr>
<tr>
<td>Geographic tongue</td>
<td>23 (4.2)</td>
<td>7.3 %</td>
<td>18.1 %</td>
<td>2(+ve)*</td>
</tr>
<tr>
<td>Atrophy of tongue papillae</td>
<td>17 (3.1)</td>
<td>5.4 %</td>
<td>13.4 %</td>
<td>1(+ve)</td>
</tr>
<tr>
<td>Geographic tongue+Fissured tongue</td>
<td>12 (2.2)</td>
<td>3.8 %</td>
<td>9.4 %</td>
<td></td>
</tr>
<tr>
<td>Tongue-tie</td>
<td>4 (0.7)</td>
<td>1.3 %</td>
<td>3.1 %</td>
<td></td>
</tr>
<tr>
<td>Total number of patients with any tongue lesion ¶</td>
<td>127 (23.3)</td>
<td>40.3 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snuff dipper’s lesion</td>
<td>30 (5.5)</td>
<td>9.5 %</td>
<td>28.8 %</td>
<td>8(+ve)</td>
</tr>
<tr>
<td>Frictional lesions</td>
<td>25 (4.6)</td>
<td>7.9 %</td>
<td>24.0 %</td>
<td>4(+ve)</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>17 (3.1)</td>
<td>5.4 %</td>
<td>16.3 %</td>
<td>5(+ve)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>16 (2.9)</td>
<td>5.1 %</td>
<td>15.4 %</td>
<td></td>
</tr>
<tr>
<td>Nicotine stomatitis</td>
<td>7 (1.3)</td>
<td>2.2 %</td>
<td>6.7 %</td>
<td></td>
</tr>
<tr>
<td>Lichen planus</td>
<td>5 (0.9)</td>
<td>1.6 %</td>
<td>4.8 %</td>
<td>3(+ve)</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>4 (0.7)</td>
<td>1.3 %</td>
<td>3.8 %</td>
<td>1(-ve)§</td>
</tr>
<tr>
<td>Unspecified nicotine stomatitis</td>
<td>3 (0.6)</td>
<td>1.0 %</td>
<td>2.9 %</td>
<td></td>
</tr>
<tr>
<td>Lichenoid lesions</td>
<td>1 (0.2)</td>
<td>0.3 %</td>
<td>1.0 %</td>
<td>1(+ve)</td>
</tr>
<tr>
<td>Total number of patients with any white lesion ¶</td>
<td>104 (19.1)</td>
<td>33.0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Red and blue lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>29 (5.3)</td>
<td>9.2 %</td>
<td>48.3 %</td>
<td>2(-ve)</td>
</tr>
<tr>
<td>Petechia</td>
<td>25 (4.6)</td>
<td>7.9 %</td>
<td>41.7 %</td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
<td>7 (1.3)</td>
<td>2.2 %</td>
<td>11.7 %</td>
<td></td>
</tr>
<tr>
<td>Hemangiomma</td>
<td>3 (0.6)</td>
<td>1.0 %</td>
<td>5.0 %</td>
<td></td>
</tr>
<tr>
<td>Total number of patients with any red and blue lesion ¶</td>
<td>60 (11)</td>
<td>19.0 %</td>
<td>100 %</td>
<td></td>
</tr>
<tr>
<td><strong>Vesiculobullous diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>15(2.8)</td>
<td>4.8 %</td>
<td>46.9 %</td>
<td>9(8+ve)</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>8(1.5)</td>
<td>2.5 %</td>
<td>25 %</td>
<td></td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>6(1.1)</td>
<td>1.9 %</td>
<td>18.7 %</td>
<td>3(-ve)</td>
</tr>
<tr>
<td>Herpes labialis</td>
<td>2(0.4)</td>
<td>0.6 %</td>
<td>6.2 %</td>
<td></td>
</tr>
<tr>
<td>Vesiculobullous lesion (not verified)</td>
<td>1(0.2)</td>
<td>0.3 %</td>
<td>3.1 %</td>
<td></td>
</tr>
<tr>
<td>Total number of patients with any vesiculobullous disease</td>
<td>32 (6)</td>
<td>10.2 %</td>
<td>100 %</td>
<td></td>
</tr>
<tr>
<td><strong>Ulcerative conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS</td>
<td>16 (2.9)</td>
<td>5.1 %</td>
<td>66.7 %</td>
<td>1(+ve)</td>
</tr>
<tr>
<td>Drug reaction</td>
<td>3 (0.6)</td>
<td>1.0 %</td>
<td>12.5 %</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>2 (0.4)</td>
<td>0.6 %</td>
<td>8.3 %</td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>1 (0.2)</td>
<td>0.3 %</td>
<td>4.2 %</td>
<td></td>
</tr>
<tr>
<td>Traumatic ulcer</td>
<td>1 (0.2)</td>
<td>0.3 %</td>
<td>4.2 %</td>
<td></td>
</tr>
<tr>
<td>Unspecified ulcer</td>
<td>1 (0.2)</td>
<td>0.3 %</td>
<td>4.2 %</td>
<td></td>
</tr>
<tr>
<td>Total number of patients with any ulcerative condition</td>
<td>24 (4.5)</td>
<td>7.6 %</td>
<td>100 %</td>
<td></td>
</tr>
<tr>
<td><strong>Pigmented Lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanotic macules</td>
<td>20 (3.7)</td>
<td>6.3 %</td>
<td>95 %</td>
<td>1(+ve)</td>
</tr>
<tr>
<td>Gingival tattoo</td>
<td>1 (0.2)</td>
<td>0.3 %</td>
<td>4.8 %</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Prevalence of oral mucosal lesions in the total group of skin diseased patients (n = 544), in the group of skin diseased patients with OML and within the 14 most frequently occurring OML groups (Continued)

<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>Total No. of Patients</th>
<th>Percentage</th>
<th>Confirmed Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroepithelial polyp</td>
<td>21 (3.9)</td>
<td>6.7</td>
<td>100</td>
</tr>
<tr>
<td>Denture induced fibrous hyperplasia</td>
<td>2 (0.4)</td>
<td>0.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Total number of patients with connective tissue lesion</td>
<td>11 (2.1)</td>
<td>3.5</td>
<td>100</td>
</tr>
<tr>
<td>Fungal infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute erythematous candidiasis</td>
<td>3 (0.6)</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
<td>3 (0.6)</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Pseudomembranous candidiasis</td>
<td>3 (0.6)</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>2 (0.4)</td>
<td>0.6</td>
<td>20</td>
</tr>
<tr>
<td>Chronic hyperplastic candidiasis</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>10</td>
</tr>
<tr>
<td>Total number of patients with any fungal infection ¶</td>
<td>10 (1.8)</td>
<td>3.2</td>
<td>100</td>
</tr>
<tr>
<td>Benign nonodontogenic tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft tumor like lesion</td>
<td>4 (0.7)</td>
<td>1.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Exostosis</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Palatal tori</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Total number of patients with any benign nonodontogenic tumor</td>
<td>6 (11)</td>
<td>1.9</td>
<td>100</td>
</tr>
<tr>
<td>Perioral lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioral dermatitis</td>
<td>4 (0.7)</td>
<td>1.3</td>
<td>80</td>
</tr>
<tr>
<td>Perioral wart</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>20</td>
</tr>
<tr>
<td>Total number of patients with any perioral lesion</td>
<td>5 (0.9)</td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>Lip lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified cheilitis</td>
<td>2 (0.4)</td>
<td>0.6</td>
<td>40</td>
</tr>
<tr>
<td>Hypopigmented lips</td>
<td>2 (0.4)</td>
<td>0.6</td>
<td>40</td>
</tr>
<tr>
<td>Cheilitis glandularis</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>20</td>
</tr>
<tr>
<td>Total number of patients with any lip lesion</td>
<td>5 (1.0)</td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>Verrucal papillary lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary hyperplasia</td>
<td>3 (0.6)</td>
<td>1.0</td>
<td>75</td>
</tr>
<tr>
<td>Focal epithelial hyperplasia</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>25</td>
</tr>
<tr>
<td>Total number of patients with any verrucal papillary lesion</td>
<td>4 (0.7)</td>
<td>1.3</td>
<td>100</td>
</tr>
<tr>
<td>Salivary gland diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocle</td>
<td>2 (0.4)</td>
<td>0.6</td>
<td>100</td>
</tr>
<tr>
<td>Total number of patients with any salivary gland disease</td>
<td>2</td>
<td></td>
<td>2(+/ve)</td>
</tr>
<tr>
<td>Malignant tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>1 (0.2)</td>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>Total number of patients with any malignant tumour</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* (+ve) = Confirmed diagnosis
§ (-ve) = Not confirmed, final diagnosis based on history and clinical picture.
¶ The sum of the categories listed may not equal the total number due to the presence of more than one lesion in one patient.

If we exclude the diagnosis of (fissured tongue + geographic tongue) as one disease entity:
- Total no. of fissured tongue will be 38 (7% of study population)
- Total no. of geographic tongue will be 35 (6.4% of study population)

If we exclude the diagnosis of (fissured tongue + geographic tongue) as one disease entity;
<table>
<thead>
<tr>
<th>Skin diseases (groups)</th>
<th>Patients with any OML (n = 315)</th>
<th>Tongue (n = 127)</th>
<th>White (n = 104)</th>
<th>Red (n = 60)</th>
<th>Vesiculobullous (n = 32)</th>
<th>Ulcerative (n = 24)</th>
<th>Pigmented (n = 21)</th>
<th>Connective (n = 11)</th>
<th>Fungal (n = 10)</th>
<th>Others (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiotic</td>
<td>59 (46.8)</td>
<td>27 (21.4)</td>
<td>22 (17.5)</td>
<td>16 (12.7)</td>
<td>3 (0.4)</td>
<td>6 (0.4)</td>
<td>-</td>
<td>-</td>
<td>1 (0.8)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Infectious lesions</td>
<td>65 (56.5)</td>
<td>25 (20.4)</td>
<td>18 (15.7)</td>
<td>12 (10.4)</td>
<td>9 (0.7)</td>
<td>5 (0.4)</td>
<td>2 (0.2)</td>
<td>3 (0.2)</td>
<td>1 (0.9)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Vesiculobullous</td>
<td>39 (72.2)</td>
<td>11 (20.4)</td>
<td>3 (05.6)</td>
<td>- (40.7)</td>
<td>22 (0.9)</td>
<td>5 (0.5)</td>
<td>3 (0.3)</td>
<td>1 (0.1)</td>
<td>4 (0.7)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>26 (54.2)</td>
<td>9 (18.8)</td>
<td>9 (18.8)</td>
<td>3 (06.3)</td>
<td>3 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.3)</td>
<td>3 (0.6)</td>
<td>- (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>24 (58.5)</td>
<td>18 (43.9)</td>
<td>7 (17.1)</td>
<td>- (17.1)</td>
<td>7 (0.4)</td>
<td>-</td>
<td>1 (0.4)</td>
<td>2 (0.4)</td>
<td>- (0.2)</td>
<td>- (0.2)</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>23 (60.5)</td>
<td>13 (34.2)</td>
<td>11 (34.2)</td>
<td>5 (13.2)</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Psoriasiform</td>
<td>17 (56.7)</td>
<td>10 (33.3)</td>
<td>7 (23.3)</td>
<td>5 (16.7)</td>
<td>- (0.3)</td>
<td>3 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Vasculopathic</td>
<td>13 (52.0)</td>
<td>8 (32.0)</td>
<td>7 (23.3)</td>
<td>2 (12.0)</td>
<td>3 (12.0)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>- (0.2)</td>
<td>- (0.2)</td>
</tr>
<tr>
<td>Tumour</td>
<td>8 (66.7)</td>
<td>3 (25.0)</td>
<td>1 (08.3)</td>
<td>- (08.3)</td>
<td>1 (08.3)</td>
<td>4 (08.3)</td>
<td>5 (08.3)</td>
<td>4 (08.3)</td>
<td>2 (16.7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Others</td>
<td>41 (74.5)</td>
<td>16 (29.1)</td>
<td>11 (20.0)</td>
<td>9 (16.4)</td>
<td>5 (01.8)</td>
<td>1 (09.1)</td>
<td>3 (07.3)</td>
<td>6 (01.8)</td>
<td>5 (01.8)</td>
<td>4 (01.8)</td>
</tr>
</tbody>
</table>

* OML (others): non odontogenic tumors, perioral lesions, lip lesions, verrucal papillary lesions, mucocele, oral malignancy

* Some patients were recorded more than one time because they appeared under more than one disease group
were the OML most frequently observed in the groups of tongue lesions, white lesions, red and blue lesions and vesiculobullous diseases, respectively.

**Study Limitations**

The present findings should be interpreted with caution due to some limitations. Patients’ refusal to volunteer for biopsy might have led to some misclassifications. Thus, some lesions that needed histological confirmation (leukoplakia, lupus erythematosus, pemphigus vulgaris, fibroepithelial polyp, chronic hyperplastic candidiasis, chelitis glandularis, focal epithelial hyperplasia, Kaposi’s sarcoma and some others) were diagnosed clinically and might contain error. Absence of standard methodological approaches and lack of agreed-upon diagnostic criteria, make comparison of epidemiological studies concerning the prevalence of OML difficult. In spite of the limitations associated with diagnostic criteria, all mucosal pathological alterations were identified in the present study.

Being a hospital based study; it is not possible to generalize from the study group to any larger population of skin diseased individuals inside or outside Khartoum. This is due to the rich geographical and socio-cultural diversity within Sudan, as well as the low utilization rate of health facilities generally observed in any developing country [31,32]. Although the KTH received patients that have been referred from all over the country, biases in the study group might have been introduced due to differing referral procedures as well as the moderate response rate.

It is unsure how close an approximation the present figures are to the prevalence of OML in the general adult population of Sudan. Probably, the rates of OML presented in this study might be overestimated both with respect to the Sudanese population in general as well as to the population of adults suffering dermatological problems. Self-selection bias was considered to influence the result of the study as patients were more likely to respond when they had OML (the characteristic of interest).

| Table 4 Skin diseases with oral lesions and with at least two OML by socio-demographic and behavioural factors (n = 544) |
|---|---|
| **Age** | Skin disease with OML | Skin disease with ≥ 2 oral lesions |
| | N = 315 | N = 113 |
| Younger (18-32 yrs) | 147 (52.7) | 42 (28.6) |
| Older (33-85 yrs) | 159 (62.4)* | 69 (43.4) |
| **Sex** | | |
| Females | 143 (52.6) | 43 (30.1) |
| Males | 172 (63.2)* | 70 (40.7) |
| **Employment status** | | |
| Employed | 197 (60.6) | 69 (35.0) |
| Non employed | 117 (53.7) | 44 (37.6) |
| **Education** | | |
| Lower education (illiterate/primary school) | 162 (60.7) | 65 (40.1) |
| Higher education | 146 (54.5) | 47 (32.2) |
| **Residence** | | |
| Khartoum | 235 (56.6) | 88 (37.4) |
| Outside Khartoum | 77 (62.1) | 24 (31.2) |
| **Medical diagnosis** | | |
| No systemic condition | 154 (51.9) | 53 (34.4) |
| Presence of systemic condition | 161 (65.2)* | 60 (37.3) |
| **Toombak use** | | |
| Never | 256 (54.8) | 90 (35.2) |
| Former/current use | 53 (77.9)** | 22 (41.5) |
| **Smoking** | | |
| Never | 251 (56.8) | 89 (35.5) |
| Former/current use | 60 (63.2) | 23 (38.3) |
| **Alcohol** | | |
| Never | 293 (57.2) | 103 (35.2) |
| Former/current use | 16 (69.6) | 9 (56.3) |

* p < 0.05 ** p < 0.00.

The sum of the categories listed may not equal the total number due to lack of information.
Moreover, with respect to the diversity of the types of OML, the present figures might be biased towards those for which people are more inclined to seek treatment, whereas other conditions are less likely to be identified in hospital based prevalence studies. Community based surveys based on random samples from the broader adult population should be recommended for future studies to estimate the actual prevalence and the health burden of OML in this country.

Since the precision of estimates tend to decrease with decreasing prevalence, the prevalence rates of rare conditions (≤ 1%) should be interpreted with particular caution. In addition, populations with different distributions of the risk factors identified for OML are not directly comparable without adjustment. Noteworthy the absence of an official patient’s medical journal has created uncertainty regarding participants’ self-reported medical condition and lifestyle patterns. A major limitation of self-reported data is recall biases in terms of underreporting of socially undesired events and a tendency to recall events as having occurred more recently than they actually did [33]. Sensitive events, tobacco and alcohol use and some medical diagnoses would probably be under reported due to social stigma and social desirability.

**Comparison of present findings with those of previous studies**

In spite of its limitations, the present study provides important information about the frequency and diversity of OML in patients with various dermatological diseases as well as the social and behavioural factors that discriminate between skin diseased patients with and without OML. Moreover, OML in the present study may appear as a part of mucocutaneous diseases, a manifestation of systemic diseases (metabolic or immunological), or an expression of drug reaction. Some OML diagnosed could be attributed to trauma, infection, or denture use, or they could be a manifestation of specific cultural habits, like use of toombak. Due to the cross sectional nature of the present study, any causal relationship could, however, not be concluded upon.

Compared with the frequency of patients with OML observed in this study (57.9%), previous ones have shown point prevalence in the range 25% - 61.6% [6,9,34-36]. Specifically, the frequency of patients with OML in the present study group was higher than those observed in the Cambodian (4.9%) [37] Malaysian (9.7%) [7], Spanish (51%) [12] and Turkish (42%) populations [36]. It was lower than that observed in population in Ljubljana (61.6%), but almost similar to the prevalence estimated in Spanish dental patients (58.7%) [8,35]. In accordance with the NHANES III [6] and the Swedish study published by Axell [5], the present study used the WHO diagnostic criteria and Axell’s diagnostic criteria [5,25]. Thus, the present results are to some extent comparable with those previous studies, in spite that NHANES III and the study by Axell used large probability samples from the general populations. The frequency observed in this study was higher than that reported in NHANES III, amounting 28% in US adults aged 17 years and above.

Consistent with the results of NHANES III and other studies, the frequency of patients with OML presented in this study varied systematically and positively with being a male and with increasing age. Other epidemiological studies have shown an opposite sex gradient or no systematic variation according to sex [9,38,39]. Sex differences in the occurrence of OML might be attributed to the high consumption of toombak by males, differences in genetic factors, social responsibility and masculinity believes [40]. Use of toombak was reported by 12.5% of the total study group. In a study emanating from northern Sudan, the frequency of toombak use was estimated to 40% (43, 44). Males adopt a more active outdoor lifestyle and are exposed to some environmental risk factors to a higher extent than women. In contrast, women are more health conscious and faster to detect abnormality in earlier stages. Older people have higher risk to develop chronic diseases in general because of increased risk with increasing age due to metabolic changes, medications, prosthetic use, and psychological problem. Moreover, economic constraints and physical status of older people may limit their access to health care services [41,42].

Epidemiological studies have revealed that tongue lesions constitute a considerable proportion of OML, with prevalence rates varying across different parts of the world. Number and type of tongue lesions involved in different studies have been an important factor in this variability. The present figure amounting to 23%, is lower than that reported in some previous studies [43,44], but higher than the rates assessed in NHANES III and in the Hungarian population [6,45]. Of interest was that 17 out of 30 patients (56.7%) with psoriasiform reaction pattern had OML and that tongue lesions (33.3%) were the most frequently occurring OML in this particular dermatological disease group (Table 3). A study of Brazilian psoriatic patients revealed that 59% presented with tongue lesions, which was the most dominant OML [46]. Similar findings have been reported by Hernandez-Perez et al [19]. With respect to fissured tongue, the total of 7% of patients with fissured tongue observed in this study corroborates the range reported previously [5,45,47,48]. Some few studies have reported high frequency of fissured tongue [35,39,43]. Over the past few years an association between geographic tongue, fissured tongue and psoriasis has been postulated. Some authors believe that it is a natural developmental anomaly and a coincidence finding [46,49] while others suggest a pathogenic relation between them [50].
Snuff dipper’s lesion was observed in 5.5% of the study group (Table 2). This frequency is higher than that reported in the American and Kenyan population (1.2% and 0.4%, respectively) [6,51], but lower than that observed in the Swedish population (15.9%) [52]. Toombak has been known to play a major role in the aetiology of oral cancer in the Sudan [23]. It contains at least 100-fold higher concentrations of the carcinogenic factor tobacco specific N-nitrosamines compared with American and Swedish commercial snuff brands [53]. A recent study showed that toombak induces DNA damage and cell death in normal human oral cells more than the Swedish snuff [54].

The frequency of oral leukoplakia (3.1%) disclosed in this study is comparable to findings from Sweden (3.6%), but higher than that reported in NHANES III (0.38%) [6]. Leukoplakia is a premalignant lesion with transformation rates varying from 15.6% to 39.2% [55]. It is highly associated with cigarette smoking [8,27,56]. Although we have not done any further analysis of smoking as a possible risk factor of leukoplakia, the low frequency rate of cigarette smoking concomitant with a relatively high frequency of oral leukoplakia as observed in this study deserves further investigation. The high frequency of leukoplakia should be taken seriously as leukoplakia in non-smokers is more likely to undergo malignant transformation than leukoplakia in smokers [55].

A total of 4 patients (0.7%) with oral manifestation of discoid lupus erythematosus (DLE) on vermilion border were diagnosed in this study (Table 2). This condition has rarely been registered in OML investigation studies. Axel [5] reported 0.01% in a Swedish population, while Ramirez et al [21] reported 5% in lupus patients referred to a dermatology clinic because of oral complaints. The difference between the present figure and that reported by Ramirez et al may be attributed to the fact that although both data were collected in dermatology clinic, the selection of patients was different. The precancerous potential of oral DLE is a controversial topic. Lu and Le [57] reported an incidence of 13.6% epithelial dysplasia in DLE. Another report from Scully et al [58] postulated that DLE on the lip showed a premalignant potential. Sun exposure plays a crucial role in the induction or exacerbation of the lupus erythematosus and actinic cheilitis [28,59,60]. In connection to that, Wakisa et al [61] reported oral cell carcinoma on lips of black patients with oral DLE. Noteworthy the tropical climate in Sudan and the summer temperature which often exceed 43°C has to be considered in interpreting such lesions.

Frequency of recurrent aphthous stomatitis (RAS) has been recorded as life time prevalence, point prevalence and as combination of both. The present study revealed a point prevalence of 2.9%, which is higher than 2% and 0.8% reported by Axell [5] and NHANES III [6] respectively. Yet, it was lower than 60% and 55% in US female student nurses and professional school students respectively [62]. This illustrates how RAS varies according to the study group examined. A number of factors have been attributed to the occurrence of this pathology, including immune dysfunction [28].

Conclusions
In conclusion, taking into consideration the selected study group and the cross-sectional design of the study, the results presented here cannot be generalized to a broader population or discussed in terms of causal relationship. The results revealed that OML were frequently diagnosed in skin diseased patients attending KTH and varied systematically with age, gender, systemic condition and use of toombak. Thus, this study provides information regarding the frequency, diversity and socio-behavioural correlates of OML of an important sub group of the Sudanese population that has never been disclosed before. Of particular significance are those lesions having a potential of malignant transformation. Accordingly, frequent and regular inspection of the oral cavity of the skin diseased patients must be emphasized. Consequently, an interdisciplinary approach in the management of such patients is highly recommended.

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Authors’ contributions
NMS was the main author conceived and designed the study, collected data, performed statistical analysis and drafted the manuscript. ANÅ was the co-supervisor, participated and guided the study design and has been actively involved in all stages throughout the work, especially statistical analyses and epidemiological analyses of data. RWA facilitated the field work and has been providing critical comments on the study design and the manuscript. HS was the main dermatologist who examined and diagnosed all the patients. ACJ was the main supervisor, supervising and guiding the whole work and confirmed and approved all the diagnosis of oral lesions. All authors read and approved the final manuscript.

Competing interests
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Influence of oral mucosal lesions and oral symptoms on oral health related quality of life in dermatological patients: a cross sectional study in Sudan

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Abstract

Background: There are only few studies considering the impact of oral mucosal lesions (OML) on the oral quality of life of patients with different dermatological conditions. This study aimed to assess the relationship between oral health-related quality of life (OHRQoL) and OML and reported oral symptoms, perceived general and oral health condition and caries experience in adult skin diseased patients attending an outpatient dermatologic clinic in Sudan.

Methods: A cross-sectional survey was carried out with 544 diagnosed skin diseased patients (mean age 37.1 years, 50 % females), during the period October 2008 to January 2009. The patients were orally examined and OML and caries experience was recorded. The patients were interviewed using the Sudanese Arabic version of the OIDP. OHRQoL was evaluated by socio-demographic and clinical correlates according to number of types of OML diagnosed (no OML, one type of OML, > one type of OML) and number and types of oral symptoms.

Results: An oral impact (OIDP > 0) was reported by 190 patients (35.6 %) (mean OIDP total score 11.6, sd = 6.7). The prevalence of any oral impact was 30.5 %, 36.7 % and 44.1 %, in patients with no OML, one type of OML and more than one type of OML, respectively. Number of types of OML and number and types of oral symptoms were consistently associated with the OIDP scores. Patients who reported bad oral health, patients with ≥ 1 dental attendance, patients with > 1 type of OML, and patients with ≥ 1 type of oral symptoms were more likely than their counterparts in the opposite groups to report any OIDP. The odds ratios (OR) were respectively; 2.9 (95 % CI 1.9-4.5), 2.3 (95 % CI 1.5-3.5), 1.8 (95 % CI 1.1-3.2) and 6.7 (95 % CI 2.6-17.5). Vesiculobullous and ulcerative lesions of OML disease groups associated statistically significantly with OIDP.

Conclusion: OIDP was more frequently affected among skin diseased patients with than without OML. The frequency of the impacts differed according to the number of type of OML, oral symptoms, and OML disease groups. Dentists and dermatologists should pay special attention to skin diseased patients because they are likely to experience oral impacts on daily performances.

Keywords: dermatology, oral mucosal lesions, oral impact on daily performance, quality of life
**Background**

Oral mucosal lesions (OML) may be the initial feature or the only clinical sign of mucocutaneous diseases, a group of mainly chronic diseases, commonly observed in a dermatologic practice [1–4]. In a previous study considering Sudanese adults with mucocutaneous diseases attending an outpatient dermatology clinic in Khartoum, the prevalence of patients with OML was high, amounting to 57.9 % [5]. Patients with OML experience a wide range of chronic and recurrent conditions that may have detrimental effect on functioning, social life and psychological well-being.

Evidently, mucocutaneous diseases have impacts on the quality of life of patients comparable to that of other medical conditions [6,7]. Patient reported outcomes in terms of oral health related quality of life (OHRQoL) measures have seldom been assessed in relation to mucocutaneous conditions [8–15]. Whereas the relationship of dental and periodontal status with OHRQoL measures have been examined across various socio-cultural contexts, few studies have considered the impact on OHRQoL of patients with disorders that are of relevance to oral medicine and dermatological practice [11,13,16,17]. This is so, although patient reported outcomes of OHRQoL may provide valuable information, for example by identifying treatment needs, selecting therapies, evaluating treatment outcomes and monitoring patient progress [18].

Several generic and disease specific OHRQoL measures have been developed to provide better understanding of the consequences of oral diseases upon quality of life and to complement traditional clinical measures [6,19]. Whereas specific OHRQoL measures assess impacts that are attributable to specific oral diseases, the generic ones take into account numerous oral conditions, some occurring simultaneously, thus providing information on the wider implications of oral status [20]. One promising generic OHRQoL measure is the Oral Impacts on Daily Performance (OIDP) scale [21,22]. The OIDP was developed to measure oral impacts that seriously affect a person’s daily life. It is based on the conceptual framework of the World Health Organisation’s International Classification of Impairments, Disabilities and Handicaps (ICIDH) [23], which has been amended for dentistry by Locker [24]. The OIDP concentrates only on the measurement of “ultimate” oral impacts, thus covering the fields of disability and handicap [22]. This inventory assesses the impact of oral conditions on basic activities and behaviours that cover the physical, psychological, and social dimensions of daily living. Considering respondent burden, the OIDP is suitable for use in population surveys and clinical practices, not only in terms of being easier when measuring behaviours rather than feeling states, but also in being short. It is originally calculated by multiplying frequency and severity scores of daily performances, providing an overall score for each OIDP item. However, applications of the weighted OIDP scores revealed no significant improvement over the use of OIDP frequency or severity scores [22]. Thus, it has been proposed to use either the frequency or the severity OIDP scores for simplicity and efficiency. Since its development, the OIDP has shown to be reliable and valid in general population based studies [25–28], as well as in studies of patients with specific oral disorders, such as traumatic injuries, periodontal disease and malocclusion [16,17,29]. Although an Arabic version of the 8 item OIDP inventory has been applied previously with Sudanese children [30] and dental attendees from a Sudanese adult population [31], this study necessitated reestablishment of its psychometrical properties. The generic OIDP inventory has yet to be applied in the context of patients with mucocutaneous diseases.

This study aimed to assess the relationship between oral health related quality of life (OHRQoL) and OML and reported oral symptoms, perceived general and oral health condition and caries experience in Sudanese adult skin diseased patients attending an outpatient dermatologic clinic in Sudan.

**Methods**

**Sampling procedure**

The present study is a part of a cross sectional hospital based study that was carried out from October 2008 to January 2009 [5]. The study was focusing on patients aged 18 years and above with mucocutaneous diseases, attending an outpatient dermatologic clinic at Khartoum Teaching Hospital (KTH). KTH is the largest national hospital in Sudan, located in Khartoum, the capital city. It is an open public and referral hospital receiving patients from all states of the country. A minimum sample size of 500 patients was calculated to estimate differences in OHRQoL between patients with and without oral mucosal lesions assuming the proportions of oral impacts to be 0.60 and 0.40 among patients with and without OML, significance level (two sided test) of 5 % and statistical power of 80 %. All patients (n = 4235) attending the outpatient facility during the survey period were invited to participate in the study. A total of 1540 subjects (36.4 %) initially accepted to participate. Fear of taking biopsy for asymptomatic lesions and time consuming examinations (oral examination, interview, and biopsy when needed) were the main reasons for not volunteering to participate. Of those who initially accepted to participate, 544 (544/1540, 35.3 %) patients were included in the study. Unexplained disappearance of patients and limited financial resources were the main reasons for withdrawal from the study. Thus, the final participation rate was 544/4235, 12.8 %. Confidentiality of the patients was maintained, participants were informed about their oral conditions, and health education was provided. Those who needed dental services were referred to the University of Science and
Technology (UST), Faculty of Dentistry, for further investigation and management. Written informed consent or finger print (illiterates) for participation and publication of the study was obtained from parents or guardians. The research conformed to the Helsinki Declaration, and ethical clearance and approval letters were obtained by the participating institutions’ committees in Sudan (UST and KTH, Department of Dermatology). In Norway, the ethical approval was obtained from the Regional Committee for Medical Research Ethics of Western Norway.

Survey instrument
A pilot study revealed a considerable number of illiterate patients, and thus a structured questionnaire was interviewer administered by two trained dentists. The interview schedule contained questions regarding socio-demographics, health and oral health related characteristics and lifestyles. The interview schedule was constructed in English and then translated and used in Arabic. Forward and backward translations were performed by two independent Sudanese professional translators in Arabic and English language. Sensitivity to culture and selection of appropriate words were considered by use of simple common Arabic words.

OHRQoL was assessed using the eight items OIDP frequency inventory [21,22]; During the past 6 months, how often have problems with your mouth and teeth caused you any difficulty with: eating and chewing food; speaking and pronouncing clearly; cleaning teeth; sleeping and relaxing; smiling and showing teeth without embarrassment; maintaining usual emotional state; carrying out major work and social role, and enjoying contact with people?. Each item was assessed using a 5-point scale: (1) Never affected; (2) Less than once a month; (3) Once or twice a month; (4) Once or twice a week; (5) Every, or nearly every day. Initially, an additive sum score (OIDP ADD) was constructed from the 8 items as originally scored (1–5, range 8–40). Secondly, each OIDP frequency item was dichotomised, yielding the categories: (0) never affected (including the original category 1), (1) affected (including the original categories 2, 3, 4, and 5). Simple count scores (SC) were created for the OIDP by adding the eight dichotomised variables. For the purpose of cross-tabulation and logistic regression analysis, the OIDP SC scores (0–8) were dichotomised as 0 = no daily performance affected and 1 = at least one daily performance affected. The distribution of the OIDP SC scores supported this cut-off point.

Socio-demographic characteristics were assessed in term of gender, age, education, tribes, marital status, and place of residence. Gender was assessed as: (1) female; (2) male. Age was recorded by asking, how old are you? and the answers were dichotomised into 2 equally sized groups; (0) 18–32 years and (1) 33 + years. Participants were classified according to their educational level using five categories: (1) illiterate; (2) primary school; (3) secondary school; (4) university; (5) higher studies. Two dummy variables were constructed yielding the categories 0 = lower education (including the original categories 1 and 2) and 1 = higher education (including the original categories 3, 4, and 5). Medical condition was assessed as a sum score of the following: heart diseases, hypertension, asthma, diabetes, liver diseases, hepatitis /jaundice, anaemia, bleeding disorders, kidney diseases, rheumatoid arthritis, allergy, cancer, epilepsy, stomach ulcer, intestinal disorders, psychiatric/mental disorders, respiratory disorders, and pregnancy. The sum scores were dichotomized into 0 = none and 1 = ≥ one. Perceived health status was recorded from (1) very bad to (4) very good. Two dummy variables were created in terms of 0 = good and 1 = bad. Perceived oral health status was measured using a 5-point rating by asking: How do you consider the present condition of your mouth and teeth? with response categories: (1) very bad; (2) bad; (3) neither good nor bad; (4) good; (5) very good. This variable was dichotomized in terms of 0 = good (including the original categories 4 and 5) and 1 = bad (including the original categories 1, 2 and 3). Reported oral symptoms were assessed by the question ‘During the previous 6 months have you experienced: dental pain/tooth- ache, abscessed tooth, dry mouth, bleeding gums, infected sore gums, tooth decay, or broken tooth. Each symptom was assessed as present (1) and absent (0). Frequency of dental attendance was assessed by asking ‘How many times have you attended a dentist during the previous 2 years?’ with response categories: (1) once; (2) twice, (3) more than twice; (4) never. A dummy bivariant was constructed yielding the response categories 1 = attended dental clinic (including the original categories 1, 2 and 3) and 0 = never attended dental clinic.

Clinical examination
Systematic comprehensive extra-oral and intra-oral clinical examinations based on visual inspection and palpation, following the World Health Organization (WHO) criteria for field surveys [32], were carried out by a dentist (NMS) who received a standard training in diagnosis of OML before the data collection (The Gade Institute, Section for Pathology, and Department of Clinical Dentistry, Section for Oral Surgery and Oral Medicine, University of Bergen, Norway). Caries experience was assessed under field conditions and scored according to the criteria described by the WHO [33]. A tooth was recorded as decayed when a cavity was apparent on visual inspection. Missing tooth was recorded if there was a history of extraction because of pain and/ or a cavity prior to extraction. DMFT, was computed as the sum of decayed, missing and filled teeth and dichotomised into caries free DMFT = 0 and having any caries experience DMFT > 0. The oral clinical examination and information with respect to OML and oral habits have been detailed elsewhere [5].
Diagnostic criteria for oral mucosal lesions
An OML was defined as any abnormal change or any swelling on the oral mucosal surface. A single lesion with confirmed diagnosis was referred to as a 'type of OML'. Diagnostic criteria for OML were based on Axell criteria and those defined in earlier studies and reviews [32,34,35].

Statistical analysis
Data were analysed using PASW Statistics version 18.0 (SPSS Inc., Chicago). Non-parametric statistics were used because the OIDP-total scores were not normally distributed. Bivariate relationships were assessed using cross-tabulation, chi-square statistics and Mann Whitney - U test.
Table 2 Percentage distribution and mean scores (SD) for the eight OIDP frequency items and the OIDP ADD score in skin diseased patients by number of types of OML

<table>
<thead>
<tr>
<th>OIDP Items</th>
<th>No OML N = 229</th>
<th>One type of OML N = 202</th>
<th>&gt; One type of OML N = 113</th>
<th>Total population N = 544</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected% (n)</td>
<td>Mean (SD)</td>
<td>Affected% (n)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Eating</td>
<td></td>
<td>26.4 (60) 1.7 (1.4)</td>
<td>33.0 (66) 2.0 (1.6)</td>
<td>39.8 (45) 2.2 (1.6)</td>
</tr>
<tr>
<td>Emotional</td>
<td></td>
<td>16.2 (37) 1.5 (1.2)</td>
<td>25.9 (51) 1.8 (1.4)</td>
<td>30.4 (34) 1.9 (1.5)</td>
</tr>
<tr>
<td>Cleaning</td>
<td></td>
<td>17.1 (39) 1.5 (1.2)</td>
<td>23.4 (46) 1.7 (1.4)</td>
<td>26.8 (30) 1.8 (1.5)</td>
</tr>
<tr>
<td>Sleeping</td>
<td></td>
<td>12.7 (29) 1.3 (1.0)</td>
<td>18.3 (36) 1.5 (1.2)</td>
<td>16.2 (18) 1.5 (1.2)</td>
</tr>
<tr>
<td>Speaking</td>
<td></td>
<td>4.80 (11) 1.1 (0.6)</td>
<td>8.0 (16) 1.2 (0.8)</td>
<td>15.9 (18) 1.4 (1.1)</td>
</tr>
<tr>
<td>Contact people</td>
<td></td>
<td>4.40 (10) 1.1 (0.6)</td>
<td>9.5 (19) 1.3 (1.0)</td>
<td>10.6 (12) 1.3 (1.0)</td>
</tr>
<tr>
<td>Major work</td>
<td></td>
<td>4.40 (10) 1.1 (0.6)</td>
<td>7.7 (15) 1.2 (0.9)</td>
<td>9.8 (11) 1.3 (1.0)</td>
</tr>
<tr>
<td>Smiling</td>
<td></td>
<td>1.8 (4) 1.0 (0.4)</td>
<td>8.5 (17) 1.2 (0.8)</td>
<td>11.5 (13) 1.4 (1.2)</td>
</tr>
<tr>
<td>OIDP &gt; 0</td>
<td></td>
<td>30.5 (69) 0.8 (1.5)</td>
<td>36.7 (72) 1.3 (2.1)</td>
<td>44.1 (49) 1.5 (2.3)</td>
</tr>
<tr>
<td>OIDP ADD</td>
<td></td>
<td>10.4 (48) 1.2 (7.2)</td>
<td>12.1 (7.2) 1.3 (8.4)</td>
<td>13.1 (8.4) 1.1 (6.7)</td>
</tr>
</tbody>
</table>

Means and % varied according to the total number of respondents in each OIDP item due to lack of information in 2–11 patients across the OIDP items.

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test. Internal consistency reliability was assessed using Cronbach’s alpha. To adjust for potential confounding factors, multiple variable logistic regression analyses were performed and OR and Nagelkerkes $R^2$ were calculated. The relationship between OIDP and number of different types of OML was assessed in unadjusted and fully adjusted models. The relationship between OIDP and each type of reported symptoms and OML disease groups was assessed in unadjusted, fully adjusted and mutually adjusted models.

**Result**

**Sample profile**

A total of 544 patients with mucocutaneous diseases participated in the present study. The mean age was 37.1 years, sd = 15.9 years (range 18–85), 50 % were females, 77 % were permanent residents of Khartoum during the previous 5 years, 47.8 % belonged to the older age group (33–85 years) and 50.1 % reported higher education. A total of 57.9 % of the patients were diagnosed with at least one clinically recognized type of OML. Full details of the prevalence of OML (types and group diseases) of the participants studied are described elsewhere [5]. A particular type of OML was recorded only once although it could be manifested at several locations in the same patient. The age of patients affected by OML ranged from 18 to 81 years, with an average of 38.6 years (sd = 16.5). A total of 6 OML group diseases, each including at least 20 patients, were recognized for the present study. *Tongue lesions* were the most frequently diagnosed OML group diseases (23.3 %) followed in descending order by *white lesions* (19.1 %), *red and blue lesions* (11 %), *vesiculobullosus diseases* (6 %), *oral ulcerative lesions* (4.5 %) and *pigmented lesions* (3.9 %). Table 1 depicts the distribution of patients’ socio-demographic, behavioural, oral symptoms and clinical features by number of types of OML. As shown, a total of 89.9 % had caries experience, 84.4 % reported more than one oral symptom and 45.5 % reported more than one systemic health condition. The most and least frequently reported conditions were tooth decay (57.1 %) and abscess (9.6 %), respectively.

**Psychometric properties of the OIDP**

In the present study, small number of missing responses (2–11) adds support to face validity of the OIDP frequency inventory. As depicted in Table 2, One hundred and ninety patients (35.6 %) perceived at least one oral impact (OIDP > 0). The mean OIDP ADD was 11.6 (sd = 6.7). The prevalence of any oral impact was 30.5 %, 36.7 % and 44.1 % in patients with respectively, no OML, one type of OML and more than one type of OML. A problem with *eating* was the most frequently reported impact. Problems with *work, contact people,* and *smiling* were the least frequently reported impacts across the three OML groups as well as in the total study group. As shown in Table 3, Cronbach’s alpha for the OIDP in the study group was 0.89 with corrected item-total correlation ranging from 0.57 (*smiling*) to 0.70 (*emotional state*). The standardized items alpha in the separate groups was 0.81 (no OML), 0.89 (one type of OML) and 0.92 (> one type of OML). The corrected item-total correlation across the three groups was above the minimum level of 0.2 required for including an item into a scale [36].

The association between the frequency of oral impacts (OIDP total >0) and factors known to be associated with oral health; socio-demographic-, clinical and behavioural variables were assessed using cross tabulation and multiple variable logistic regression analyses. As depicted in Table 4, the frequency of subjects having at least one impact (OIDP > 0) increased significantly with increasing number of types of OML both in unadjusted and adjusted analysis with subjects having more than one type of OML being about twice as likely as their counterparts without OML to report oral...
impacts (OR 1.8 (95 % CI 1.1-3.2). Perceived oral health status remained statistically significantly associated with OIDP after having included all variables in the model. Multiple logistic regression analysis revealed that socio-demographic, behavioural variables and medical conditions entered in the first step explained 20 % of the variance (Nagelkerke $R^2 = 0.20$). Entering number of types of OML in step 2 raised the explainable variance by 1 % (Nagelkerke $R^2 = 0.21$).

As shown in Table 5, six out of eight specific symptoms were associated with impaired OHRQoL in adjusted logistic regression analyses. When all reported symptoms were accounted for, only OML pain (OR 10.3, 95 % CI 4.2-25.4), infected sore gums (OR 4.1, 95 % CI 1.9-8.6), dental pain (OR 3.1, 95 % CI 1.8-5.3) and tooth decay (OR 1.8, 95 % CI 1.0-3.1) remained statistically significantly associated with OIDP. Pain associated with mucosal lesion had the strongest impact OR 10.2 (95 % CI 4.2-25.0), and dry mouth the weakest impact OR 0.9 (95 % CI 0.4-1.7) on OIDP. As depicted in Table 6, the OML disease groups of vesiculo-bullous and ulcerative lesions discriminated statistically significantly between subjects with and without OIDP in adjusted as well as in mutually adjusted logistic regression analyses. A total of 72.4 % versus 33.5 % ($p < 0.001$) of the participants with and without vesiculobullous lesions and 77.3 % versus 33.9 % of participants with and without oral ulcerative lesions ($p < 0.001$) had oral impacts on their daily performances. When adjusting for socio-demographics, subjects with vesiculobullous lesions were 7.4 times OR 7.4 (95 % CI 2.9-18.8) and subjects with oral ulcerative lesions were 5.7 times OR 5.7 (95 % CI 1.9-16.9) more likely than their counterparts without those OML disease groups to report oral impacts. The corresponding mutually adjusted ORs were 8.2 (95 % CI 3.2-20.9) and 6.7 (95 % CI 2.2-20.0).

Discussion

This is the first study considering OHRQoL in patients with various mucocutaneous diseases, using an Arabic version of the OIDP frequency inventory. Arabic versions of OHRQoL instruments such as the Oral Health Impact Profile (OHIP-14), the Geriatric Oral Health Assessment Index (GOHAI) and the OHQoL-UK inventory have been reported to be reliable and valid for use in adult populations from Saudi Arabia, Egypt and Syria [37–39]. The results of this study indicate that, when used with patients having mucocutaneous diseases, the Arabic OIDP version is valid and reliable demonstrating psychometric properties similar to the original English version [27] as well as the Thai [26], Greek [28] and Norwegian versions of the OIDP [40]. Moreover, the OIDP has shown to be usable across various subgroups of the Sudanese population [30,31], first applied as a self-administered questionnaire in dental attendees from the general population, secondly in personal interviews with schoolchildren and more recently in personal interviews with patients in a dermatologic clinic. Thus, internal consistency reliability in terms of Cronbach’s alphas of 0.89 was satisfactory and well above the recommended level of 0.70 [36]. Moreover, the corrected item-total correlation coefficients were above the

| Table 3 Corrected item total correlation and Cronbach’s alpha of OIDP by number of types of OML |
|-----------------------------------------------|---------------------|---------------------|
| No OML (N = 226) | Cronbach’s Alpha (Standardized Items) = 0.811 |
| **OIDP items** | **Corrected Item-Total Correlation** | **Cronbach’s Alpha if Item Deleted** |
| Eating | .675 | .757 |
| Speaking | .447 | .792 |
| Cleaning | .592 | .767 |
| Smiling | .269 | .808 |
| Sleeping | .634 | .759 |
| Emotional state | .655 | .755 |
| Carrying out major work | .564 | .779 |
| Contact | .391 | .796 |
| One type of OML (N = 196) | Cronbach’s Alpha (Standardized Items) = 0.894 |
| Eating | .721 | .867 |
| Speaking | .586 | .878 |
| Cleaning | .713 | .865 |
| Smiling | .614 | .876 |
| Sleeping | .715 | .865 |
| Emotional state | .680 | .870 |
| Carrying out major work | .646 | .874 |
| Contact | .683 | .870 |
| > One type of OML (N = 111) | Cronbach’s Alpha (Standardized Items) = 0.921 |
| Eating | .700 | .909 |
| Speaking | .711 | .906 |
| Cleaning | .751 | .902 |
| Smiling | .657 | .910 |
| Sleeping | .751 | .902 |
| Emotional state | .779 | .900 |
| Carrying out major work | .766 | .903 |
| Contact | .747 | .904 |
| Total study population (N = 533) | Cronbach’s Alpha (Standardized Items) = 0.890 |
| Eating | .694 | .863 |
| Speaking | .606 | .869 |
| Cleaning | .692 | .859 |
| Smiling | .572 | .872 |
| Sleeping | .698 | .858 |
| Emotional state | .703 | .858 |
| Carrying out major work | .671 | .864 |
| Contact | .642 | .866 |
minimum level of 0.20 for inclusion of an item into a scale across patients with and without OML [36]. Although no approach guarantees cross-cultural equivalence, the Arabic version of OIDP seemed to preserve the overall concepts of the English version and did not differ in terms of sequence of questions, the Likert scale and the recall memory period (6 months) used. Notably, the respondents had few difficulties in completing the 8 item OIDP interview. This highlights the feasibility of employing the Arabic version of the OIDP frequency inventory in oral medicine and dermatologic clinical settings in Sudan. Recognizing the frequency and severity of the OIDP scores to have similar predictive power, using the OIDP frequency score in this study, should be the better single choice because of its better reproducibility [22]. However, the degree of impact could not be accounted for by this model. According to the present results, the frequency of oral impacts varied systematically and in the expected direction with self-reported oral health status, clinical dentition status and number of reported oral symptoms across patients having none, at least one and more than one type of OML. Moreover, patients having more than one type of OML were more likely to report oral impacts than their counterparts without OML and with only one type of OML. Notably, cross-sectional studies cannot provide definite information about cause-and-effect relationships since both predictor and outcome variables have been measured at the same point in time. Longitudinal studies are needed to improve the interpretation of factors influencing OIDP in adult patients with OML. The moderate fit of the overall multivariable model indicates that other essential variables were not included in the model. Types of OML have fluctuated from asymptomatic lesions (snuff dipper lesions) to the most chronic and painful one (oral pemphigus vulgaris) [5].

### Table 4 Unadjusted and adjusted associations of OIDP with socio-demographics, behaviours and number of types of OML in skin diseased patients (n = 544). Percentage (n), odds ratio (OR) and 95 % Confidence Interval (CI)

<table>
<thead>
<tr>
<th>Variables</th>
<th>OIDP &gt; 0N = 190% (n)</th>
<th>Unadjusted OR (95 % CI)</th>
<th>Adjusted OR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30.7 (81)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>40.5 (109)*</td>
<td>1.5 (1.0-2.2)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-32 yr</td>
<td>34.7 (95)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>33-85 yr</td>
<td>36.4 (91)</td>
<td>1.0 (0.7-1.5)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>31.2 (82)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Higher</td>
<td>39.3 (103)*</td>
<td>1.4 (0.9-2.0)</td>
<td>1.4 (0.9-2.3)</td>
</tr>
<tr>
<td>Perceived oral health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>24.5 (82)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bad</td>
<td>54.8 (108)**</td>
<td>3.7 (2.5-5.4)</td>
<td>2.9 (1.9-4.5)**</td>
</tr>
<tr>
<td>Perceived health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>30.5 (110)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bad</td>
<td>46.7 (79)**</td>
<td>2.0 (1.3-2.9)</td>
<td>1.5 (0.99-2.4)**</td>
</tr>
<tr>
<td>Dental attendance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never attended dental clinic</td>
<td>27.4 (90)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Attended dental clinic</td>
<td>48.8 (98)**</td>
<td>2.5 (1.7-3.6)</td>
<td>2.3 (1.5-3.5)**</td>
</tr>
<tr>
<td>Medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>30.1 (87)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>At least one</td>
<td>42.2 (103)*</td>
<td>1.6 (1.1-2.4)</td>
<td>1.3 (0.8-2.1)</td>
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<tr>
<td>Number of types of OML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>30.5 (69)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>One</td>
<td>36.7 (72)</td>
<td>1.2 (0.7-1.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;one</td>
<td>44.1 (49)*</td>
<td>1.8 (1.1-3.2)*</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.001, * p = 0.05

♯ Number of types of OML: no OML (p = 0.06), one type OML (p = 0.3), > one type OML (p = 0.02)

The sum of the categories listed may not equal the total number due to lack of information.
Both type and number of reported oral symptoms discriminated between patients with and without oral impacts (OIDP > 0). Dental attendance was one of the strongest predictors of oral impact in this study. The association between dental attendance and improved oral health has been widely documented [42]. However, in this study, dental attendance was associated with deteriorated OHRQoL. That pattern might reflect perceived treatment need among the study population [43]. This is consistent with results reported previously [44,45]. Although pain was the second less commonly reported symptom, it emerged as the strongest predictor of oral impacts among the symptoms investigated both in adjusted and mutually adjusted logistic regression analyses. This is consistent with the multidimensional nature of pain that affect physical, social and psychological well-being [10,46]. In the context of oral health, oral pain influences eating, drinking, and other oral everyday activities. Conversely, the highly prevalent condition of tooth decay had a small negative impact on OIDP. This might be attributed to the fact that patients learn to cope with commonly occurring symptoms and conditions that become less disabling with recurrence.

The present results corroborate findings with other OHRQoL measures. Generic OHRQoL measures...
OHRQoL-UK measure and OHIP-14 were proven to be valid and reliable in patients with oral lichen planus (OLP) [10]. Moreover, oral health in patients with symptomatic OLP was reported to have an increased burden on their life quality compared to those with non-symptomatic OLP. Mc Grath et al [8] found that patients with ulcers, erosions and symptomatic oral lesions had bad OHIP-14 scores, suggesting that they had increased quality of life impairments compared to their counterparts with non-symptomatic lesions. Similar results have been presented in studies of patients with Behçet’s disease using the OHIP-14 inventory [47].

In another study of UK patients, attending an outpatient oral medicine clinic, Llewellyn et al [9] found that patients with stomatological disease to have higher levels of functional limitations, physical pain and psychological discomfort than the general population. Oral ulceration associated with Behçet’s disease and recurrent aphthous stomatitis (RAS) have been reported to impair life satisfaction and the performance of daily activities [11,13]. A Spanish study comparing OHRQoL in patients with OLP with healthy controls concluded that impairments were greatest in the former group of patients across all dimensions of the OHIP inventory [14]. According to this study results, about 30-40 % of the patients with the OML disease groups of tongue lesions, white lesions, red and blue lesions and pigmented lesions reported oral impacts. On the other hand, the impact frequency among patients suffering oral ulcerative conditions and vesiculobullous diseases amounted to 77 % and 72 %, respectively. A previous study revealed that RAS and pemphigus vulgaris were the most frequently occurring diagnosis among oral ulcerative conditions and vesiculobullous diseases in mucocutaneous diseased patients attending the KTH [5]. Evidence that RAS has the highest impact on patients’ quality of life as compared to other oral mucosal diseases in dermatology patients has been shown elsewhere [13]. The present findings suggest that practitioners should notify type and number of OML and reported symptoms when making their treatment plan for this category of patients.

This study suggests that Sudanese patients with mucocutaneous diseases suffer moderate impairments of their OHRQoL, which is measureable by the Arabic version of the generic OIDP inventory. Moreover, eating, emotional problems and cleaning were the most frequently reported impacts, followed by problems with sleeping and speaking across subjects with and without OML. This compares to what has been observed among subjects with other medical conditions as well as with subjects from

<table>
<thead>
<tr>
<th>OML disease groups</th>
<th>N</th>
<th>OIDP &gt; 0N = 190% (n)</th>
<th>Unadjusted OR (95 % CI)</th>
<th>AdjustedaOR (95 % CI)</th>
<th>Mutually adjustedbOR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue lesions</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>417</td>
<td>34.8 (142)</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>38.4 (48)</td>
<td>1.1 (0.7-1.7)</td>
<td>1.0 (0.6-1.6)</td>
<td></td>
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<tr>
<td>White lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>440</td>
<td>34.7 (149)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>104</td>
<td>39.8 (41)</td>
<td>1.2 (0.8-1.9)</td>
<td>1.3 (0.7-2.1)</td>
<td></td>
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<tr>
<td>Red and blue lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>484</td>
<td>36.1 (171)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>32.3 (19)</td>
<td>0.8 (0.4-1.4)</td>
<td>0.9 (0.9-1.0)</td>
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<tr>
<td>Vesiculobullous lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>513</td>
<td>33.5 (169)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>72.4 (21)**</td>
<td>5.2 (2.2-11.9)</td>
<td>7.4 (2.9-18.8)**</td>
<td>8.2 (3.2-20.9)**</td>
</tr>
<tr>
<td>Oral ulcerative lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>520</td>
<td>33.9 (173)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>77.3 (17)**</td>
<td>6.6 (2.4-18.3)</td>
<td>5.7 (1.9-16.9)*</td>
<td>6.7 (2.2-20.0)*</td>
</tr>
<tr>
<td>Pigmented lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>523</td>
<td>35.7 (183)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>35.0 (7)</td>
<td>0.9 (0.3-2.4)</td>
<td>0.7 (0.2-2.3)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.001

a) Adjusted for sex, age, education, perceived health status, dental attendance and medical condition.
b) Adjusted for sex, age, education, perceived health status, dental attendance, medical condition and other OML disease groups.

The sum of the categories listed may not equal the total number due to lack of information.
the general adult population in developed and developing countries [25,40,48]. The present frequency of OIDP ranging from 30 % to 44 % is comparable to the estimates of a national Greek survey (39 %), but is higher than those reported from national surveys in Norway (18 %) and Great Britain (12 %) [28,40]. On the other hand, this figure is lower than those observed in older adults in other cultures (50-60 %) [26], and from dental attendees in Khartoum (79 %) [31]. The present figures are also lower than those observed among Swedish adult patients (50-54 %) reporting regular medication according to the Anatomical Therapeutic Chemical classification system and having specific diagnoses of diseases categorized according to the WHO International Classification of Diseases, the ICID-10 [48].

Some limitations should be considered when interpreting the results. First, the cross sectional design restricts ability to make inferences with respect to the direction of the observed associations. Secondly, being a hospital based study; it is not possible to generalize findings to any larger population of mucocutaneous diseased individuals inside or outside Khartoum. Nevertheless, as KTH is the largest public main referral hospital in Sudan, receiving patients referred from all district in Sudan, the dermatology clinic-outpatients may capture the variety in characteristic of patients with skin diseases. In addition, self-reports and a recall period of 6 months can result in underestimation of health consequences, but might provide valid estimate for ultimate impact [49]. Self-selection and non-response bias might have influenced the results as patients were probably more likely to respond when they had OML. The present study suffered from lack of information regarding non-responders and thus non-response biases are difficult to estimate. Moreover, with respect to the diversity of the types of OML, the present figures might be biased towards those for which people are more inclined to seek treatment, whereas other conditions are less likely to be identified in hospital based prevalence studies. Absence of normative OIDP scores of the general Sudanese adult population, further limits possibility to use the general population as control group. Moreover, it should be acknowledged that the observations related to specific types of OML disease groups were based on small numbers and that the reported impacts cannot be attributed to specific diseases, symptoms and lesions. On the other hand, the generic OIDP scores might be compared across oral diseases and across specific patient groups and the general population. A generic OHRQoL instrument, such as the OIDP could help dermatologists to detect oral impacts, improve the patient doctor communication and provide the basis for better management of the dermatological patients, involving patients’ as well as the doctors’ perspectives.

Conclusions

OIDP was more frequently affected among skin diseased patients with than without OML. The frequency of the impacts differed according to the number of type of OML, oral symptoms, and OML disease groups. Dentists and dermatologists should pay special attention to skin diseased patients because they are likely to experience oral impacts on daily performances.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

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Author details


Authors’ contributions

NMS was the main author conceived and designed the study, collected data, performed statistical analysis and drafted the manuscript. ACJ was supervising and guiding the whole work and confirmed and approved all the diagnosis of oral lesions. RWA facilitated the field work. HS was the main supervisor of the present study, participated and guided the study design and has been actively involved in all stages throughout the work, especially statistical analyses and epidemiological analyses of data. All authors read and approved the final manuscript.

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References


Clinical and histological characterization of oral pemphigus lesions in patients with skin diseases: a cross sectional study from Sudan

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Abstract

Background: Pemphigus is a rare group of life-threatening mucocutaneous autoimmune blistering diseases. Frequently, oral lesions precede the cutaneous ones. This study aimed to describe clinical and histological features of oral pemphigus lesions in patients aged 18 years and above, attending outpatient's facility of Khartoum Teaching Hospital - Dermatology Clinic, Sudan. In addition, the study aimed to assess the diagnostic significance of routine histolopathology along with immunohistochemical (IHC) examination of formalin-fixed, paraffin-embedded biopsy specimens in patients with oral pemphigus.

Methods: A cross-sectional hospital-based study was conducted from October 2008 to January 2009. A total of 588 patients with confirmed disease diagnosis completed an oral examination and a personal interview. Clinical evaluations supported with histopathology were the methods of diagnosis. IHC was used to confirm the diagnosis. Location, size, and pain of oral lesions were used to measure the oral disease activity.

Results: Twenty-one patients were diagnosed with pemphigus vulgaris (PV), 19 of them (mean age: 43.0; range: 20–72 yrs) presented with oral manifestations. Pemphigus foliaceus was diagnosed in one patient. Buccal mucosa was the most commonly affected site. Exclusive oral lesions were detected in 14.2% (3/21). In patients who experienced both skin and oral lesion during their life time, 50.0% (9/18) had oral mucosa as the initial site of involvement, 33.3% (6/18) had skin as the primary site, and simultaneous involvement of both skin and oral mucosa was reported by 5.5% (1/18). Two patients did not provide information regarding the initial site of involvement. Oral lesion activity score was higher in those who reported to live outside Khartoum state, were outdoor workers, had lower education and belonged to Central and Western tribes compared with their counterparts. Histologically, all tissues except one had suprabasal cleft and acantholytic cells. IHC revealed IgG and C3 intercellularly in the epithelium.

Conclusions: PV was the predominating subtype of pemphigus in this study. The majority of patients with PV presented with oral lesions. Clinical and histological pictures of oral PV are in good agreement with the literature. IHC confirmed all diagnoses of PV.

Keywords: Oral pemphigus, Skin disease, Histology, Immunohistochemistry, Sudan

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Background

Pemphigus is a group of chronic inflammatory autoimmune bullous diseases. Although rare, they are potentially life-threatening diseases that are associated with high morbidity and mortality, if not properly treated [1,2]. The disease is associated with immunoglobulin (Ig) G and complement factor (C) 3 antibodies against intercellular adhesion structural components in the epithelium [3]. The immune reaction eventually breaks down the adhesion components and leads to epithelial cell detachment, which is clinically seen as intraepithelial blisters, erosions or ulcers in the skin and mucous membranes [4]. The underlying cause and activating mechanism that initiates the immune response is unidentified. However, both genetic and environmental factors have been postulated to play a role in the pathogenesis of pemphigus [5]. In this context, social habits like use of traditional cosmetics and smoking have been implicated [6-8].

Pemphigus has several subtypes, of which three have been associated with oral mucosal involvement: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus [9]. The first two subtypes are differing with respect to the localization of intraepithelial blisters. In PV, the blisters are located suprabasally, while in PF they are more superficially located. Paraneoplastic pemphigus, although uncommon, is associated with internal malignant neoplasia [10].

Oral lesions present as vesicles or bullae that quickly break, leaving painful erosions or ulcers with irregular borders; they most often affect buccal mucosa and gingivae and heal slowly, without scarring. In PV, the oral lesions are reported as the initial sign of the disease in 50% of patients, yet these oral lesions have the greatest resistance to efficient treatment.

PV is the most predominant type of pemphigus, affects middle-aged adults without gender predilection [9,11-16] and has an incidence varying from 0.76 to 32 per million inhabitants per year [17-19]. While PV is a prevailing diagnosis in the Mediterranean region, South Asia and in the Jewish population [20,21], it is a rare disease in Northern Europe, USA, South Africa and northern region of Africa [6,18,19,22-24]. Reports from Mali and South Africa have shown that PV is rare in the black ethnicity [22,24].

Diagnosis of pemphigus is based on careful correlation of disease history and clinical findings with histopathologic characteristics. Direct immunofluorescence (DIF) on sections from a fresh frozen biopsy or indirect immunofluorescence (IIF) performed on patient’s serum are important for verifying the diagnosis [25]. However, in situations where IF is difficult to perform, immunohistochemistry (IHC) on formalin-fixed tissue samples may be an alternative test to confirm the diagnosis [26].

A study conducted in a dermatology clinic of Khartoum Teaching Hospital (KTH) in Sudan in 1998, focusing mainly on skin lesions, showed that PV was the dominant variant of pemphigus, constituting 88% of all cases diagnosed [27]. According to that study, oral mucosa was the second most common site of the lesion to occur after the trunk. The highest frequency of PV was found in the third decade of life [27]. Another study conducted in the same clinic in 2008, revealed a prevalence of oral PV of 2.8% among skin diseased outpatient attendees [28]. This study also showed that the frequency of oral PV among patients with skin disease with any oral mucosal lesions was 4.8%. In both studies, clinical information and conventional histological examination of biopsies using haematoxylin and eosin (H&E) staining were the only methods for diagnosing skin lesions.

Sudan is a large country with a multi-cultural multi-ethnic society. The prevailing ethnicities are Arabic and African, with hundreds of tribal divisions. The epidemiologic profile is typical of Sub-Saharan African countries; malaria, infectious diseases, hypertension, diabetes mellitus, and nutrition disorders are among the prominent diseases treated in the health units of Sudan [29]. On the basis of these considerations and due to the scarce information available regarding pemphigus in sub-Saharan African populations, the present study, presenting a further analysis of the data conducted in 2008 [28], aimed to describe clinical presentation of patients with oral pemphigus attending the dermatologic clinic of KTH. Given the fact that conventional histology was the only diagnostic tool in public hospitals in Sudan, the study also evaluated the diagnostic significance of combining this technique with IHC analysis of the formalin-fixed, paraffin-embedded oral biopsy specimens.

Methods

Sampling procedure

A cross sectional hospital based study was carried out focusing on patients aged ≥18 years with mucocutaneous diseases, attending an outpatient dermatologic clinic at KTH from October 2008 to January 2009. KTH is the largest national hospital in Sudan, located in Khartoum, the capital city. It is an open public and referral hospital, receiving patients from all the states of the country. For the present study, a minimum sample size of 500 patients was calculated based on an assumed prevalence of oral mucosal lesions (OML) in patients with skin diseases of 5%, a confidence interval of 95%, and an absolute precision of 0.02 [30]. All patients (n = 4235) attending the outpatient facility during the survey period were invited to participate in the study. A total of 1540 subjects (36.4%) initially accepted to participate. Fear of taking biopsy for asymptomatic lesions and
time consuming examinations (oral examination, interview, and biopsy when needed) were the main reasons for not volunteering to participate. Of those who initially accepted to participate, 588 (588/1540, 38.1%) patients were finally included in the study.

Confidentiality of the patients was maintained, participants were informed about their oral conditions, and health education was provided. Those who needed dental services were referred to the clinics of the Faculty of Dentistry, University of Science and Technology (UST), Umdurman, for further investigation and management. Written informed consent or finger print (illiterates) for participation and publication of the study was obtained from patients or their parents/guardians. The research conformed to the Helsinki Declaration, and ethical clearance and approval letters were obtained from the participating institutions’ committees in Sudan (UST and KTH, Department of Dermatology) and Norway (The Regional Committee for Medical Research Ethics of Western Norway).

**Socio-demographic characteristics and clinical examination**

A structured questionnaire was administered by two trained dentists in face to face interviews. **Socio-demographic characteristics** were measured in terms of gender, age, tribe, occupation, marital status, place of residence and oral habits. Participants were also asked about history of PV among first-degree relatives (parents, grandparents, siblings, children, and grandchildren). Medical condition and treatment were assessed according to the following conditions: heart diseases, hypertension, asthma, diabetes, liver diseases, hepatitis /jaundice, anaemia, bleeding disorders, kidney diseases, rheumatoid arthritis, allergy, cancer, epilepsy, stomach ulcer, intestinal disorders, respiratory disorders, pregnancy, psychiatric treatment, radiotherapy and chemotherapy. Furthermore, the patients were asked if their medical condition was diagnosed by a specialist and if they were under medication.

An expert dermatologist (HS) evaluated the patient’s skin diseases based on history of the disease and clinical findings, and the diagnosis was subsequently confirmed by histological examination when it was considered necessary. Details of involved sites at presentation and clinical course of the lesions were registered.

Systematic comprehensive extra-oral and intra-oral clinical examinations based on visual inspection and palpation, following the World Health Organization (WHO) criteria for field surveys [31], were carried out by a dentist (NMS) who received a training in diagnosis of OML before the data collection (The Gade Institute, Section for Pathology, and Department of Clinical Dentistry, Section for Oral Surgery and Oral Medicine, University of Bergen, Norway). An OML was defined as any abnormal change or any swelling in the oral mucosal surface. Diagnostic criteria for OML were based on Axell’s criteria and those defined in former studies and reviews [31-33]. The oral clinical examination and additional information with respect to OML and oral habits have been reported elsewhere [28]. Data on location, size, clinical presentation of the oral lesion (vesicle, erosion/ulcer) and clinical course were recorded. Skin lesions and oral lesions were encountered during the survey and were photographed using a digital camera (Canon EOS 400D). Final diagnoses of all biopsies were given by an expert oral pathologist (ACJ).

**Assessment of clinical oral lesions’ activity**

To assess the clinical severity of the oral lesions, an oral lesion activity score (OLAS) was constructed. The score was based on three components. Firstly, clinical extension of the OML was assessed. A modified system based on an established protocol [34] was used to register the extension of an oral lesion at10 anatomical locations; upper lip, lower lip, gingival mucosa, unilateral buccal mucosa, bilateral buccal mucosa, tongue, floor of the mouth, hard palate, soft palate and oropharynx. Each location was assessed as 0 = no lesion, 1 = presence of lesion, resulting in a total score ranging from 0 to 10. Secondly, size of the lesion was determined according to the largest diameter of a lesion at any location present at examination and scored as; 1 < 1 cm, 2 ≥ 1 cm. Thirdly, severity of symptoms was evaluated by asking patients to describe any pain associated with eating and drinking and was reported as: 0 = no pain, 1 = mild to moderate pain, and 2 = severe pain. Based on a former report [35], the OLAS for each patient was constructed as the sum of objective score (location, size) and subjective score (pain), ranging from 1 to 14, and reported in terms of means.

**Assessment of oral tissue biopsy**

Oral tissue biopsies were taken from the periphery of the lesions. The tissue was fixed in formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin (H&E) and examined using light microscope. To evaluate inflammation, number of inflammatory cells (mononuclear and polymorphonuclear cells) in the superficial parts of the connective tissue adjacent to the tip of the epithelial rete ridges, were counted in 6 random fields (one field = 250 μm²) per section using an ocular grid and high power magnification (40 ×). The inflammatory cells were counted 3 times per each field, and results were expressed as a mean per specimen (mean ± SD/1500 μm²). The variation of degree of inflammation between specimens was evaluated.
Procedure for immunohistochemistry on formalin-fixed, paraffin-embedded oral tissue

IHC for IgG and C3 was performed on formalin-fixed, paraffin-embedded oral mucosal specimens from 11 patients. Sections, 4 μm-thick, were cut on a Leica RM2155 microtome and mounted on glass slides (Super Frost Plus, Gerhard Menzel Gmbh, Germany) and heated at 56°C overnight. The sections were deparaffinized in xylene and rehydrated in alcohol. For C3c, sections were incubated in target retrieval solution (pH6, S1699, DAKO, Glostrup, Denmark), microwaved for 15 minutes after the buffer had come to a boil, then left to cool down on bench and thereafter washed slightly under running tap water for 5 minutes. Primary anti-human C3c polyclonal rabbit compliment (A0062, DAKO) at 1:15000 dilutions was incubated for 30 minutes at room temperature. For IgG, sections were incubated in epitope retrieval solution (proteinase type XXIV bacterial, Sigma P 8038 37) for 10 minutes at 37°C. Primary antibody polyclonal rabbit anti-human IgG (A 0423, DAKO) at 1:60000 dilutions was incubated for 60 minutes. Endogenous peroxidase activity was blocked by 0.03% hydrogen peroxide (H₂O₂) for 10 minutes at 37°C. Primary antibody polyclonal rabbit anti-human IgG (A 0423, DAKO) at 1:60000 dilutions were incubated for 30 minutes at room temperature. For IgG, sections were incubated in epitope retrieval solution (proteinase type XXIV bacterial, Sigma P 8038 37) for 10 minutes at 37°C. Primary antibody polyclonal rabbit anti-human IgG (A 0423, DAKO) at 1:60000 dilutions were incubated for 30 minutes at room temperature. For IgG, sections were incubated in epitope retrieval solution (proteinase type XXIV bacterial, Sigma P 8038 37) for 10 minutes at 37°C. Primary antibody polyclonal rabbit anti-human IgG (A 0423, DAKO) at 1:60000 dilutions were incubated for 30 minutes at room temperature. 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Statistical analysis

Descriptive statistical analysis was done using PASW Statistics version 18.0 (SPSS Inc., Chicago, USA).

Results

A total of 588 outpatients participated in the study. Out of those participants, there were 22 patients with pemphigus, where PV was the most frequent disease (95.4%, 21/22) followed by PF (4.5%, 1/22). Fourteen patients (63.6%, 14/22) were already diagnosed, coming with new active lesions, while 7 patients (31.8%, 7/22) were newly diagnosed cases. In one patient there was no information about disease history. Of the 588 patients, 359 had at least one type of OML, while oral PV was registered in 19 patients.

Demographic features of patients with oral PV

Of the 19 patients diagnosed with oral PV (mean age 43.0, range 20–72 yrs), 10 were females (mean age, 35.8 yrs) and 9 were males (mean age, 38.3 yrs). None of the females were pregnant. As shown in Table 1, the majority of the patients were <50 yrs (68.4%), low education (84.2%), married (77.8%), had outdoor jobs (52.6%), and were residing outside the Khartoum state (57.9%). Patients who reported Western tribes were 47.4% (9/19) compared to 21% (4/19) from Northern tribes, 26.3% (5/19) from Central tribes and only one reported Southern tribes. Totals of 11.1%, 21.1%, and 10.5% confirmed use of toombak, smoking and use of alcohol, respectively. These habits were exclusively reported by males.

History and aggravating factors

Negative family history (first degree- relatives) was reported by all patients. The systemic conditions reported by the patients included hypertension (5 patients), intestinal problems (4 patients), and allergy, anaemia, arthritis, and diabetes each was reported by 3 patients. Moreover, peptic ulcer, hepatitis, thyroid and liver diseases were reported by one patient each. No neoplastic diseases were recorded. Aggravating factors like eating spicy food, stress and smoking were reported by 3 patients. Concerning medications, one patient had taken penicillin and another one co-trimoxazole before eruption of the disease. All patients were scheduled to be treated with systemic steroids.

Clinical presentation of oral lesions of PV

At time of examination, 76.1% (16/21) of the patients with PV had both oral and skin lesions. Exclusively oral lesions were observed in three females 14.2% (3/21), and a former history of skin lesions was reported by two of them. In patients who experienced both skin and oral lesions during their life time, 50.0% (9/18) had oral mucosa as the initial site of involvement, 33.3% (6/18) had skin as the primary site, and simultaneous involvement of both skin and oral mucosa was reported by 5.5% (1/18). Two patients did not provide information regarding the initial site of involvement. In addition to oral lesions, extremities and trunk were the most common cutaneous sites involved followed by scalp, genitalia and eyes. As shown in Figure 1, bilateral buccal mucosa was the most commonly affected site followed by hard palate. The sites least affected were oropharynx and unilateral buccal mucosa. The clinically predominant oral lesions were mucosal erosions and ulcers. Vesicles were evident in one patient only.

Oral lesions which were > 1 cm in diameter were registered in 52.6% (10/19), and those which were ≤ 1 cm in diameter were registered in 47.4% (9/19) of patients. Pain was reported as severe by 43.8% (7/16), moderate by 37.5% (6/16) and no pain by 16.7% (3/18) of patients. Missing information was noted in each category of pain description. With respect to the OLAS total scores, scores 3 and 4 were registered in one patient each.
(6.3%), while 6, 7, 8, 9, 11, 12 and 13 total scores were recorded in two patients each (12.5%). The total mean of the OLAS was 8.27 (range 3–13).

As shown in Table 1, the mean of the OLAS was high with those who resided out of Khartoum state and with outdoor workers (10.2) compared with those living in Khartoum state (6.1) and indoor workers (6.7). Also, it was high with lower education (9.3) compared to higher education (6.0), and with those who reported Central (10.6) and Western (9.6) tribes compared to other tribes from Northern and Southern parts of Sudan.

### Microscopic examination

Eleven out of 16 patients with oral lesions agreed to have a biopsy taken. The histological characteristics were comparable in all tissue specimens. Ten out of eleven biopsies were covered by non-keratinized epithelium. Few inflammatory cells (lymphocytes and neutrophils) were present in the superficial epithelial layer of 5 biopsies. No candida hyphae could be demonstrated by PAS staining. Nearly all biopsies demonstrated spongiosis in the lower spinous cell layers, in addition to presence of neutrophils and lymphocytes in 6 biopsies. Apoptotic cells were seen in the spinous layer of 3 specimens. Suprabasal epithelial clefts were detected in 10 out of 11 biopsies, while one patient biopsy showed spongiosis only. However, in that patient, the diagnosis of PV was based on histopathology of a skin biopsy. In some sections, 1 to 2 layers of suprabasal keratinocytes were attached to basal cells forming part of floor of the cleft. In 6 biopsies, the clefts were especially seen on the tip of the epithelial rete ridges (Figure 2). The basal cells

<table>
<thead>
<tr>
<th>Age</th>
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<th>Male</th>
<th>OLAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>8 (80.0)</td>
<td>5 (55.6)</td>
<td>11 (8.7 ± 3.5)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>2 (20.0)</td>
<td>4 (44.4)</td>
<td>5 (8.6 ± 2.3)</td>
</tr>
</tbody>
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<table>
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<th>Education</th>
<th>Female</th>
<th>Male</th>
<th>OLAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low education (illiterate + primary)</td>
<td>9 (90.0)</td>
<td>7 (77.8)</td>
<td>13 (9.3 ± 2.8)</td>
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<tr>
<td>High education</td>
<td>1 (10.0)</td>
<td>2 (22.2)</td>
<td>3 (6.0 ± 3.0)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Female</th>
<th>Male</th>
<th>OLAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmarried</td>
<td>2 (20.0)</td>
<td>2 (25.0)</td>
<td>4 (8.0 ± 3.7)</td>
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<tr>
<td>Married</td>
<td>8 (80.0)</td>
<td>6 (75.0)</td>
<td>11 (8.7 ± 3.1)</td>
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</table>

<table>
<thead>
<tr>
<th>Occupation</th>
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<th>Male</th>
<th>OLAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor job (professional, skilled labour and unemployment)</td>
<td>6 (60.0)</td>
<td>3 (33.3)</td>
<td>7 (6.7 ± 3.2)</td>
</tr>
<tr>
<td>Outdoor job (farmer, animal breeder, street seller and builder)</td>
<td>4 (40.0)</td>
<td>6 (66.7)</td>
<td>9 (10.2 ± 2.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tribal distribution</th>
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<th>Male</th>
<th>OLAS (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern region</td>
<td>2 (20.0)</td>
<td>2 (22.2)</td>
<td>4 (5.7 ± 2.0)</td>
</tr>
<tr>
<td>Southern region</td>
<td>1 (10.0)</td>
<td>0</td>
<td>1 (7.0)</td>
</tr>
<tr>
<td>Western region</td>
<td>5 (50.0)</td>
<td>4 (44.4)</td>
<td>8 (9.6 ± 3.0)</td>
</tr>
<tr>
<td>Central region</td>
<td>2 (20.0)</td>
<td>3 (33.3)</td>
<td>3 (10.6 ± 2.5)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Residence during last 5 years</th>
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<th>Male</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Khartoum state</td>
<td>5 (50.0)</td>
<td>3 (33.3)</td>
<td>6 (6.1 ± 2.3)</td>
</tr>
<tr>
<td>Out of Khartoum state</td>
<td>5 (50.0)</td>
<td>6 (66.7)</td>
<td>10 (10.2 ± 2.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Habits</th>
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<th>Male</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Toombak user</td>
<td>0</td>
<td>2 (25.0)</td>
<td>1 (6.0)</td>
</tr>
<tr>
<td>Non-user</td>
<td>10 (100)</td>
<td>6 (75.0)</td>
<td>14 (8.8 ± 3.2)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0</td>
<td>4 (44.4)</td>
<td>4 (8.0 ± 0.8)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>10 (100)</td>
<td>5 (55.6)</td>
<td>12 (8.9 ± 3.5)</td>
</tr>
<tr>
<td>Alcohol user</td>
<td>0</td>
<td>2 (22.2)</td>
<td>2 (7.5 ± 0.7)</td>
</tr>
<tr>
<td>Non-user</td>
<td>10 (100)</td>
<td>7 (77.8)</td>
<td>14 (8.8 ± 3.3)</td>
</tr>
</tbody>
</table>

The total number in the different categories did not add to 19 owing to missing values.
forming the floor of the cleft varied between areas in the same section as well as between sections, displaying complete loss of intercellular attachment (tombstones) or showing intact attachment, where all basal cells remaining attached to the basement membrane and lamina propria. Inside the cleft, partially and completely detached keratinocytes (acantholytic cells) from the basal and lower prickle cells layers were spotted as single cells or clusters. In addition, lymphocytes and neutrophils were the main inflammatory cells inside the cleft.

In all tissue sections, the superficial parts of the connective tissue were characterized by edema, small blood vessels, loose fiber arrangements and both interstitial and perivascular inflammatory infiltrates. Mononuclear cells were the principal inflammatory cells, and there were only few neutrophils and eosinophils. The total number of mononuclear cells varied across the 6 fields for each specimen (Table 2), from 151 cells (mean: 25.1 ± 4.2; range: 22–31 cells) to 407 cells (mean: 67.8 ± 10.2; range: 53–79 cells). Mononuclear cells in the specimens were not influenced by the level of the OLAS. Deeper in the connective tissue, mast cells and perivascular mononuclear cell infiltrates were seen in 7 specimens.

**Immunohistochemistry**

IgG and C3 were detected intercellularly in the epithelium of all specimens examined. The staining was strongest in the suprabasal layer of the epithelium (Figures 3 and 4).

**Discussion**

This is the first study to report on the clinical characteristics of patients with oral pemphigus in Sudan, specifically in outpatients of a dermatology clinic in KTH. In this study, the prevailing variant of pemphigus was PV (95.4%), and oral mucosal involvement was present in 90.4% of the patients. An initial oral involvement was reported by 50% of those with both skin and oral lesions. The majority of the patients were in their fifth decade of life. Palate and buccal mucosa were the most common locations followed by tongue and lower lip. Based on the OLAS, the highest severity of the oral lesions was found in patients with low education, having outdoor jobs, from Central and Western tribes, living out of Khartoum state and being non-smokers. The histopathological pictures of all specimens were in agreement with the IHC findings. However, our findings should be interpreted with caution since several limitations were inherited in
the study design. The cross-sectional hospital based design of this study and the small sample size of the study populations hindered statistical evaluation of the findings. In addition, the relatively short period for data collection and the potential effect of selection bias were considered to influence the results and limit generalization. While the KTH is one of the largest national referral hospitals in Sudan, other referral and private hospitals could also receive patients from other parts of Khartoum and the rest of the country. In spite of the limitations mentioned above, the study may be beneficial as a first step in studying a new issue and to generate hypotheses.

Pemphigus is primarily considered to be a dermatologic disease. The fact that PV commonly and initially affects the oral mucosa and then the skin [16], gives dentists a great opportunity to detect the disease at an early stage. The present study showed that 90.4% of the patients had oral mucosal lesions, which is in accordance with a previous report [36]. Moreover, a multicentre study by Brenner et al. [37], found varying prevalence of oral lesions in patients with PV; 66% in Bulgarian patients, 83% in Italian, and 92% in Israeli patients. Our result is higher than those reported by Ramirez et al. [38], who found a prevalence of 18% of oral lesions in PV patients examined in a dermatologic clinic in Mexico City.

Generally, PV has been reported to affect men and women equally [9]. Several studies registered the highest frequency in females [21,39-46], while a few studies have reported males’ dominance [41,47]. In general, estrogen (exogenous and endogenous) has been accused for the females’ predominance in autoimmune diseases [48]. Supporting the hypothesis, 80% of the females in the

<table>
<thead>
<tr>
<th>Patients</th>
<th>Area 1</th>
<th>Area 2</th>
<th>Area 3</th>
<th>Area 4</th>
<th>Area 5</th>
<th>Area 6</th>
<th>Sum (Mean ± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>26</td>
<td>32</td>
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<td>38</td>
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<tr>
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<td>40</td>
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<td>33</td>
<td>35</td>
<td>44</td>
<td>38</td>
<td>235 (39.1 ± 4.7)</td>
<td>33–45</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>22</td>
<td>22</td>
<td>31</td>
<td>22</td>
<td>24</td>
<td>151 (25.1 ± 4.2)</td>
<td>22–31</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>15</td>
<td>18</td>
<td>39</td>
<td>43</td>
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<tr>
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<td>16</td>
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<td>48</td>
<td>28</td>
<td>49</td>
<td>42</td>
<td>46</td>
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<td>28–49</td>
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<td>19</td>
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<td>29</td>
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<td>53</td>
<td>79</td>
<td>77</td>
<td>73</td>
<td>60</td>
<td>65</td>
<td>407 (67.8 ± 10.2)</td>
<td>53–79</td>
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<td>75</td>
<td>38</td>
<td>45</td>
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<td>73</td>
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<tr>
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<td>70</td>
<td>50</td>
<td>50</td>
<td>24</td>
<td>47</td>
<td>60</td>
<td>301 (50.1 ± 15.3)</td>
<td>24–70</td>
</tr>
</tbody>
</table>

Figure 3 Immunohistochemistry staining used to detect IgG in formalin-fixed, paraffin-embedded oral tissue biopsy from patients with pemphigus vulgaris. IgG (brown colour) is seen in the intercellular junction of keratinocytes reliable with the location of desmoglein 3 (scale = 50 μm).

Figure 4 Immunohistochemistry staining used to detect C3 in formalin-fixed, paraffin-embedded oral tissue biopsy from patients with pemphigus vulgaris. C3 (brown colour) is seen in the intercellular junction of keratinocytes reliable with the location of desmoglein 3 (scale = 50 μm).
present study were in the premenopausal period (< 50 years old). A prospective case–control study among Tunisian females found that traditional cosmetics, commonly used after marriage (henna, kohl, souak), was associated with occurrence of pemphigus diseases in younger women [6]. In that respect, we found that 80% of women were married. Sudanese married women use on daily basis traditional home-made cosmetics like skin exfoliating scrub paste, oils, perfumes, henna, and smoke-baths, beside modern cosmetic skin whiteners, which are used among both married and single women.

Evidences from Western countries indicate that autoimmune diseases are increasing in frequency and show a female predominance [48,49]. Accordingly, some authors hypothesized that this could be, at least partially, attributable to new or modified patterns of exposure to chemicals, including environmental estrogens [48]. Many organochlorine pesticides are suspected to impair natural hormonal function in organisms by mimicking endogenous estrogen. The hypothesis proposes that the impact of pesticides and gardening materials on estrogen metabolism can trigger pemphigus. Our result showed that among outdoor workers, farming was the outdoor job most frequently reported. One may speculate that beside sun exposure, environmental estrogens may affect specific population with a susceptible genetic background.

Traditionally, PV tends to appear between the ages of 40 and 60 years [9]. In the present study the mean age was 43 years, close to findings from Thailand, Spain and Korea [15,42,50], but lower when compared with data given from countries like Romania, Germany and North America [51-53] and higher than other countries like Kuwait and Iran [14,54].

Educational achievement is connected with better employment and income, which in turn can affect health behaviors and access to health facilities and thus treatment in appropriate time [55]. That could partially explain the higher frequency of PV and the higher OLAS mean values among the low educated group as well as outdoor job workers in comparison to their counterpart. In addition, outdoor workers are likely to be exposed to sun light and UV radiation for a long time of the day. The band of the UV radiation has been suggested to induce pemphigus [56,57]. Also, heat might be necessary to liberate a sufficient amount of PV antigen from epithelium [58]. Moreover, mid latitude, subtropical and tropical countries have been suspected to have higher frequency of pemphigus than other countries. Thus, higher incidence was found in Mediterranean countries [20,59] compared to high latitude countries like Finland and North America [18,19]. An epidemiological study from Greece demonstrated that high temperatures and extreme sun exposure raise the relapse frequency of PV [59]. Another study from South Africa observed exacerbation of pemphigus during summer time [24]. In connection with that, Sudan is located between latitude 4 to 22 degrees north, characterized by an environment range from tropical climate in the south, to savannah and desert in the central and northern area where temperature normally exceeds 40ºC, especially during summer [60,61].

Controversially, one study from Iran showed that higher rate of disease onset was in winter [54]. Another study from Tehran found that there was no significant difference of disease onset or recurrence among annual seasons, indicating that genetic and racial variations might play a more important role than climate differences in the pathogenesis of PV [62].

PV was the predominant variant of pemphigus in the present study (95.4%). This was in accordance with several previous studies [11-15], but opposing data from some African regions (Mali, South Africa, Tunisia and Libya) where PF was the dominant variant [22-24,63]. The data from Mali and South Africa proposed that PV is rarely seen in black African ethnicity. Sudan has two ethnic groups; Afro-Arab tribes and non-Arab African tribes, where Southern tribes belong to the latter one. In the present result, PV was registered in only one patient from Southern tribes of Sudan compared to 9 (47.4%) from Western tribes (Afro-Arab and non-Arab African tribes). Yet the disease was not registered in Sudanese Eastern tribes (non-Arab African tribes) which lead to unexplained results. Several heterogeneous factors have been implicated of inducing or triggering pemphigus in different ethnic populations including genetic factors, in particular Human Leukocyte Antigen (HLA) class II loci. That has been noted in Ashkenazi Jews, Iranian, Italian patients and also in patients of South Asian and Mediterranean origin [64,65]. In comparison, the disease seems to be rare in Northern Europe and USA. However, genetic factors alone is not enough to initiate the autoimmune reaction as demonstrated by a report of PV in only one of two monozygotic twins [66]. Our data showed an absence of PV in first degree relationship. This is supported by the paucity of familial PV reports in the literature as reviewed by Tetsuya et al. [67]. It is conceivable that exogenous factors might induce PV in genetically predisposed individuals.

Cigarette smoking has been a highly controversial topic with respect to effect on certain autoimmune diseases. Although it is considered one of the leading morbidity and mortality risk factors [68], some clinical evidence has supported its beneficial and protective effect on patients with pemphigus [69] and certain diseases such as ulcerative colitis and recurrent aphthous ulcers [70,71]. Thus, smoking history is an essential factor in pemphigus patients. A case control study by Brenner et al. [37], reported that risk for PV was lower in current and ex-smokers than for patients who had never smoked. It has been shown that
short-term exposure to nicotine might control keratinocyte adhesion by increased motility, proliferation and lateral migration. That would increase re-epithelialization and rapid wound healing. On the other hand, opposite results were shown when patients were subjected to chronic or long-term exposure to nicotine [72,73]. The effect of chronic exposure to nicotine was shown to reduce cutaneous blood flow and inhibit and decrease fibroblast migration in wound healing and to induce wound infection [74,75]. Moreover, immunosuppressive effects in terms of reduction in immunoglobulins, helper/ suppressor T-cell ratios, lymphocyte transformation and natural killer cell cytotoxicity could also delay the healing process. Nevertheless, varying outcomes are still recorded [76]. In association with that, the present study showed that smoking was exclusively reported by males and in only 21.1% (4/19) of the patients. Although non-smokers and smokers registered similar OLAS means, the latter were the least frequent.

In this study, patient’s medical history revealed some medications that were taken before the disease eruption such as penicillin, co-trimoxazole and anti-hypertensive drugs, indicating a possible association, which has also been suggested in other studies [5,77,78].

The present results showed that half of the patients with oral lesions had experienced the first lesion in the mouth followed by skin lesions. This is in accordance with a study performed in India (53.5%) [79]. The 14.2% (3/21) of patients with exclusively oral lesion found in our study is comparable to 16.5% from Iran [80], but in contrast to 86% found in Northern Greece [44]. Exclusively oral lesions tend to be a marker for less virulent disease and a better prognosis [81]. It is uncommon to clinically identify vesicles or bullae in the oral mucosa due to continuous mechanical forces that characterize the normal activity of the mouth. Beside the thin and fragile roof of the PV bullae, irregular erosions and ill-defined ulcers were the principal clinical features of oral PV. Our findings notified only one patient with bullae, contradicting a Brazilian study that found a rate of 75% of patients with clinically identifiable vesicles [82]. The distribution of oral lesions in our PV patients followed the international literature showing the most common sites were palate, buccal mucosa, tongue and lower lip [83]. Other studies found the gingiva to be the most commonly affected site [84,85]. Although gingival lesions are uncommon at the onset, they usually manifest as severe desquamative or erosive gingivitis in advanced stages of PV [86].

Based on histology, we were able to confirm the diagnosis in 10 out of 11 specimens. The microscopic examination was found to be comparable with the classic histology of PV as described in the literature. This result reinforces previous suggestions, that oral lesions of pemphigus preserve the histologic features of acantholysis more than in skin lesions, and they are less prone to bacterial infections than skin, where secondary infections may affect the definitive histologic pattern [87]. Oral ulcers were the main clinical characteristic features of the patients in this study. Therefore, to demonstrate the typical pathologic changes in PV, all specimens in the present study were taken from intact oral mucosa immediately adjacent to the lesions. Considering inflammatory infiltrates, the results showed that mononuclear cells were the principal inflammatory cells in all specimens, confirming the chronic nature of PV. Furthermore, evidences have shown that lymphocytes play a critical role in immune surveillance and activation in PV. Lymphocytes have been reported to produce specific cytokines that may be critical for the launch and continuation of the production of Dsg3-specific autoantibodies by B lymphocytes [88,89]. Our results showed moderate variations in the numbers and means of inflammatory cells from one specimen to another, as well as in the range of cells within one specimen. These results are in consistence with the literature [10].

Tzanck smear to detect acantholytic cells is used as a screening procedure and rapid test for diagnosing oral PV [90]. A recent report has shown that Candida smear using methylene blue was useful in detecting acantholytic cells in such cases [91]. Some studies found that the efficacy of H&E staining alone in diagnosing PV is probably greater than 90% and could be considered satisfactory [92,93]. However, ambiguous cases and treatment planning remain challenging. Equivocal cases come from a number of conditions that are expressed as oral vesicles or bullae that rapidly rupture and result in erosions or ulcers. Some are viral infections such as herpes simplex infection, while others are immunologic diseases like pemphigus, pemphigoid, lupus erythematosus and lichen planus. In such cases, DIF and IIF are important to discriminate between them, confirm diagnosis and plan proper treatment. Limitations of these techniques are the availability of blood serum or fresh frozen tissue that requires specific facilities to perform, and they do not always exist in all health services, especially in developing countries. It also is important to secure safe transport to laboratories using correct media that prevent autolysis of the tissue. In addition, it is costly and thus not affordable for all patients. Thus, pathologists in Sudan usually receive patients’ specimens that have been fixed in formalin or normal saline [94]. To overcome these limitations, a previous study applied DIF on formalin-fixed, paraffin-embedded tissue [95]. Although the technique was less sensitive than when using frozen tissue, the possibility of misclassification was low. Another study using immunoperoxidase staining technique on formalin-fixed, paraffin-embedded tissue from PV
patients, proved the possibility of detecting immunoglobulin in the absence of microscopic features of the disease [96]. Our study demonstrates that IHC on formalin-fixed, paraffin-embedded tissue is a reliable method to confirm the diagnosis of PV. At the time of the present study, and specifically in public hospitals in Sudan, confirmation of the PV was based on clinical examination, anamnesis and conventional histopathology. Thus, IHC enhances the accuracy of diagnosing PV and can be used when only formalin-fixed, paraffin-embedded tissue is available for analysis.

Conclusion
PV was the predominating subtype of pemphigus in this study. The majority of PV presented with oral lesions. The results of this study are in agreement with the previous studies with respect to the age, gender, oral lesions distribution and first presentation of PV. The aetiology of PV is uncertain, but several heterogeneous factors could implicate to its pathogenicity. IHC in formalin-fixed, paraffin-embedded oral tissue biopsy confirmed the diagnosis of PV. The current study shed light on the higher prevalence of oral PV among the study population, suggesting that great collaboration efforts between dermatologists and dentists would provide better treatment and avoid serious sequelae and death.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
NMS was the main author who conceived and designed the study, collected data, performed statistical analysis and drafted the manuscript. ANÅ participated in the study design, statistical and epidemiological data analyses. RWA facilitated the field work. HS was the main dermatologist who examined and diagnosed all the patients. ACJ was the main-supervisor, participated and guided the study design and confirmed and approved all the diagnosis of oral lesions. All authors read and approved the final manuscript.

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