THE PREVALENCE AND IMPACT OF ORAL LESIONS ON THE QUALITY OF LIFE IN PERSONS WITH EPIDERMOLYSIS BULLOSA

by

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ABSTRACT

Introduction

Hereditary Epidermolysis bullosa (EB) is a group of rare mechanobullous dermatological disorders in which blisters develop following gene mutations. These genes encode structural proteins that anchor the epidermis to the underlying dermis. There are four main types of Epidermolysis bullosa, with more than 20 subtypes. The medical, physical and psychosocial aspects of Epidermolysis bullosa are well documented (**Lucky *et al,* 2005; Mellerio *et al,* 2005**). Many studies have documented case reports of associated oral lesions (**Silva *et al,* 2004; Pacheco and de Sousa Araugio 2008; Siqueira *et al,* 2008).** However, no assessment of the impact of these oral lesions on the affected person's everyday life has been made. The morbidity of the oral lesions associated with EB is expected to have an impact on the quality of life of these patients.

Aim

To assess the prevalence and impact of oral lesions on daily activities in persons with Epidermolysis bullosa in Cape Town, South Africa, utilizing the Oral Impact on Daily Performance (OIDP) measure.

Research Design and Methodology

A case-controlled, descriptive analysis of the way in which oral lesions impact on quality of life in persons with Epidermolysis bullosa was carried out using semi-structured interviews. Fourteen persons with a confirmed diagnosis of hereditary Epidermolysis bullosa who attended the dermatology clinics at the Red Cross and Groote Schuur hospitals participated in the study. The control group comprised eighteen persons closely matched for gender, age, and dental status. Three persons with EB were unavailable for inclusion in the study.

Results and Discussion

Fourteen persons with Epidermolysis bullosa and eighteen controls were included in the study. Epidermolysis bullosa Simplex comprised the largest sub-group (n=9). Two persons had Junctional Epidermolysis bullosa, two had recessive Dystrophic Epidermolysis bullosa and one person had Kindler syndrome.

The oral manifestations observed were consistent with those reported in the literature (**Chimenos *et al,* 2003; Silva *et al,* 2004; Pekinar *et al,* 2005**). No significant oral lesions (other than tooth decay) were seen in persons in the Epidermolysis bullosa Simplex group. Oral ulcers, atrophy of the dorsal surface of the tongue and gingival erythema were seen in persons with Junctional Epidermolysis Bullosa. The two individuals with Dystrophic Epidermolysis bullosa had a maximal oral opening of 15mm and 24mm. Ankyloglossia, depapillation of the dorsal tongue, absence of palatal rugae and poor oral hygiene was seen in these two persons. The patient with Kindler syndrome presented with erythematous and inflamed gingiva and cratering in the maxillary anterior interdental area. The gingiva appeared desquamative, fragile and bled with even the slightest provocation. Healing peri-oral blisters and angular cheilitis was also seen. His mouth opening was restricted to a maximal oral aperture of 13mm and his tongue extrusion was limited to only the tip of the tongue passing over the lower anterior incisor teeth.

Defects in the tooth enamel was recorded in both participants with Junctional Epidermolysis bullosa and one person with dystrophic Epidermolysis bullosa, as well as excessive occlussal tooth wear (attrition), which may have been secondary to enamel hypoplasia. The dental caries status of the Epidermolysis bullosa and control groups varied according to age. The dmf for persons with Epidermolysis bullosa (all of whom had Epidermolysis bullosa Simplex), was lower than in the control group. The DMF in EB persons (15.3) was higher than in the control group (10.1).

Toothache and tooth decay were the most common perceived complaints in both the Epidermolysis bullosa and control participants, accounting for the high overall OIDP

score in both groups (87.5%). No statistically significant difference was found between the two groups (85.7% and 88.9% for Epidermolysis bullosa and control group persons respectively).

Conclusion

The results of the study show that oral lesions (particularly tooth decay and toothache) in persons with Epidermolysis bullosa do affect their daily activities and the impact thereof is high. Other oral manifestations, irrespective of the subtype, had little impact on the OIDP score. This may be because the EB persons become tolerant of and "learn to cope" with them.

Recommendations

Epidermolysis bullosa is a rare condition and not all persons with EB will present with lesions. However, all health personnel (including oral health profession) must be cognizant of this condition, in order to manage these persons safely, without incurring harm inadvertently. Thus, the overall management of persons with Epidermolysis bullosa must encompass ways to minimize and prevent trauma; provide an optimum wound healing environment; provide pain management and judicious checks for the development of premalignant lesions. This necessitates a multidisciplinary and holistic approach, with emphasis on patient involvement. To this end, an oral health care programme should form an integral part of their management because of the risk of dental disease. Periodic recall visits will enable the monitoring of home care and minimize the need for advanced restorative procedures. In this way, one may reduce the impact any oral problems may have, so that they do not further influence the patients well being.

Keywords

Epidermolysis bullosa, oral lesions, quality of life

DECLARATION

I, the undersigned hereby declare that the work contained in this dissertation is my original work and that it has not been previously in its entirety or in part submitted at any university for a degree.

…… ……..

Haly Karen Holmes Date

The work presented in this mini-thesis was undertaken in the
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Cape Town

DEDICATION

For my husband and children - Brent, Sarah and David.
None of this would have been possible without your
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CONTENTS **Page**

LIST OF TABLES **Page**

LIST OF FIGURES **Page**

ABBREVIATION S USED IN THIS MINI-THESIS

EB	**Epidermolysis bullosa**
EBS	**Epidermolysis bullosa Simplex**
DEB	**Dystrophic Epidermolysis bullosa**
DSP	**Desmoplakin**
DDEB	**Autosomal Dominant Dystrophic Epidermolysis bullosa**
RDEB	**Autosomal Recessive Dystrophic Epidermolysis bullosa**
EBSS	**Epidermolysis bullosa Simplex Superficialis**
EB-LOC	**Epidermolysis bullosa localized**
EB-DM	**Epidermolysis bullosa Dowling Meara**
EB gen-nonDM	**Epidermolysis bullosa Simplex, generalized**
EBS-MP	**Epidermolysis bullosa Simplex with mottled pigmentation**
EBS-MD	**Epidermolysis bullosa Simplex with muscular dystrophy**
EBS-PA	**Epidermolysis bullosa Simplex with pyloric atresia**
EBS-AR	**Epidermolysis bullosa Simplex, autosomal recessive**
EBS-Og	**Epidermolysis bullosa Simplex, Ogna**
EBS-migr	**Epidermolysis bullosa, migratory circinate**
IFM	**Immunofluorescence Mapping**
JEB	**Junctional Epidermolysis bullosa**
JEB-H	**Junctional Epidermolysis bullosa, Herlitz**
JEB-O	**Junctional Epidermolysis bullosa, non-Herlitz**
OHRQoL	**Oral health related quality of life measures**
OIDP	**Oral Impact on Daily Performances**
TEM	**Transmission Electron Microscopy**
PKP	**Plakophilin**
KRT5	**Keratin-5**
KRT14	**Keratin-14**
KIND	**Kindlin-1**
LAM	**Laminin**
PLEC1	**Plectin**

CHAPTER 1: INTRODUCTION

1.1. Structure of the report

For the benefit of the reader, this text will outline the format of this report describing the oral manifestations seen in fourteen persons with Epidermolysis bullosa and how they perceive these lesions to affect their daily activities. This mini-thesis comprises five chapters, describing the various aspects investigated. Chapter 1 summarizes the background and purpose for the study. Chapter 2 details the literature review, including a concise overview of the most recent classification of Epidermolysis bullosa types and subtypes; salient clinical features associated with the various forms of EB as well as diagnostic techniques used. A summary of international case reports is included, documenting the type and prevalence of oral lesions reported in the various Epidermolysis bullosa types. Lastly, a summary of the quality of life assessment tool (OIDP) used in the study is presented.

Chapter 3 lists the study aim and objectives. Chapter 4 discusses the research design and methodology used, describing the research tool and data collection method. Chapter 5, Chapter 6 and Chapter 7 detail the study results, discussion and conclusion respectively.

1.2.Background and purpose of the study

Hereditary Epidermolysis bullosa (EB) is a group of rare mechanobullous dermatological disorders, with an autosomal dominant or recessive mode of transmission. Blisters develop following mutation of genes, which encode structural proteins within the epidermis, or those that anchor the epidermis to the underlying dermis. Four main types exist with more than 20 subtypes, each distinguished based on their clinical manifestations, inheritance pattern, ultra- structural findings and implicated gene(s) (**Fine *et al,* 2008**). The target pathology may be supra-basal (Epidermolysis bullosa Simplex); at the junction between the dermis and the epidermis (Junctional Epidermolysis bullosa); sub-basal (Dystrophic Epidermolysis bullosa); or have mixed cleavage planes (Kindler syndrome) (**Pekinar *et al,* 2007; Fine *et al,* 1989; 2008**).

Clinically, Epidermolysis bullosa is characterized by skin fragility and diverse variability exists within the phenotypic spectrum of the condition (**Mellerio *et al,* 2007**). Blisters arise most commonly following minor trauma or spontaneously (**Winship, 1986; Pfender *et al,* 2005)**. The clinical features range from mild blisters localized to the hands and feet, to severe generalized mucocutaneous blistering (**Pekinar *et al,* 2007; Pfender *et al,* 2007**). Dystrophic Epidermolysis bullosa is often associated with significant scarring which can cause relative microstomia due to oral contractures.

The medical, physical and psychosocial aspects of Epidermolysis bullosa are well documented (**Fine *et al,* 2008; Van Scheppingen *et al,* 2008**). Oral lesions may have an impact on the quality of life of patients, as well as their nutritional status. The integral role of interdisciplinary care in attaining a good quality of life for the affected persons, cannot be overemphasized (**Lucky, *et al* 2005)**. Many international studies have documented case reports of oral lesions associated with Epidermolysis bullosa subtypes (**Silva *et al,* 2004; Pacheco and Araugio 2008; Siqueira *et al,* 2008)** however, the impact of these oral lesions in everyday life of the affected persons has not been assessed. The subtypes of EB in South African families have been delineated and published as part of a doctoral thesis (**Winship, 1986**), but no record of their oral status has been reported.

Slade and Spencer in 1997 (**Sanders *et al,* 2006**), developed an assessment tool named the Oral Impact on Daily Performance (OIDP), which was designed to measure the impact of socio-dental factors on daily activities. It would complement the normative clinical measures and allow a broader assessment of the way in which oral changes impact on patients' quality of life. The value of employing such a tool allows one to associate the impact to specific oral lesions that require attention, potentially provide more insight into consequences of untreated oral lesions and highlight the benefits of dental treatment.

CHAPTER 2: LITERATURE REVIEW

Many advances with regard to the spectrum and classification of inherited Epidermolysis bullosa have been made and most recently, a Consensus Classification group redefined the heritable Epidermolysis bullosa types and subtypes. These include: Epidermolysis bullosa Simplex; Junctional Epidermolysis bullosa; Dystrophic Epidermolysis bullosa and Kindler syndrome (**Fine *et al*, 2008**).

2.1. DIAGNOSIS OF EPIDERMOLYSIS BULLOSA

The clinical diagnosis of Epidermolysis bullosa in a neonate or mildly affected adult is challenging for the following reasons (**Uitto and Richard, 2005).**

1. it mimics other vesiculobullous conditions
2. the initial generalized blistering may later resolve into a more localized Epidermolysis bullosa subtype (inverse type in particular)
3. some newborns with severe generalized manifestations, may manifest as a milder localized Epidermolysis bullosa type later on

A biopsy of clinically unaffected skin is mandatory for a diagnosis of EB. The level of tissue separation correlates with the affected epidermal protein components and is subtype dependant. Currently two laboratory techniques are employed to identify the cleavage plane within the skin of suspected Epidermolysis bullosa persons. These include transmission electron microscopy and immunofluorescence mapping. A third diagnostic technique (DNA mutational analysis) is reserved for prenatal diagnosis (**Pfender *et al*, 2005**).

2.1.1. Transmission Electron Microscopy (TEM) – (Mihai and Sitaru, 2007)

The main advantage of electron microscopy (EM) is that it allows visualization of specific proteins within the skin. There are differences in the number or appearance of specific proteins in the various subtypes of Epidermolysis bullosa. These structures include desmosomes, keratin filaments, hemi-desmosomes, sub-basal dense plates, anchoring filaments and anchoring fibrils. This technique however, does not allow

assessment of alterations in antigenicity, because for assessment by EM, the tissue must be fixed in gluteraldehyde. The proteins involved in anchoring the epidermis to the underlying dermis have discreet locations and an additional procedure called antigenic immunofluorescence mapping allows assessment of the location of the protein (i.e. either within the roof or base of the blister).

EM is extremely technique sensitive and can be misleading if performed by inexperienced clinicians and laboratories (**Fine *et al,* 2008**). It is however, the only non-molecular laboratory technique that can identify persons with Dowling Meara Epidermolysis bullosa Simplex, a rare subtype (**Uitto and Richard, 2005**).

2.1.2. Immunofluorescence Mapping (IFM)

IFM is diagnostically as reliable as EM for some of the Epidermolysis bullosa subtypes. Specimens harvested from fresh spontaneous or traction induced blisters are transported in specific IFM transport media. The cryo-preserved skin specimens are exposed to a panel of antibodies (such as bullous pemphigoid antigen, laminin-1, type IV collagen and keratin 14). In addition, monoclonal and polyclonal antibodies to laminin-332 (formerly laminin-5), type VII collagen, type XVII collagen, plectin, α*6β*4 integrin and keratin 14 may be applied to Epidermolysis bullosa skin sections to elucidate alterations in their relative expression and distribution within the skin. The degree of antibody staining is semi-quantitative and cannot be exclusively used to distinguish between the Epidermolysis bullosa subtypes within a tissue specimen. Thus, its use should be reserved as a primary laboratory marker for diagnosis of suspected Epidermolysis bullosa persons and used prior to mutational analysis (**Fine *et al,* 2008**).

IFM has the following advantages over EM:

1. It is less expensive and simpler to perform
2. The tissues can be processed within a few hours and the specific transport media preserves tissue antigenicity for several weeks at a given temperature.

2.1.3. *DNA Mutational analysis*

DNA mutational analysis is the most accurate method in determining the mode of inheritance as well as the exact location and type of inherent molecular mutation. Future gene therapy will be dependant hereon. IFM should be the primary laboratory marker for diagnosis because there are too many possible genes that need to be screened before identifying where the ultrastructural defect lies (epidermis, lamina lucida, or sub-lamina densa). In addition, not all the "mutational hotspots" have been identified for every Epidermolysis bullosa type or subtype. Identification of these sites will require entire gene sequencing to determine the mutation and more than one gene may be implicated in the same phenotype. In addition, the fact that not all mutations have been identified in every Epidermolysis bullosa patient, suggests the presence of unidentified genes. Lastly, genotype-phenotype correlation is only predictable in the Epidermolysis bullosa Simplex type. In addition to all the points mentioned above, DNA testing is expensive and technique sensitive, with very few capable laboratories available worldwide (**Fine *et al,* 2008**). Even though DNA testing is the most accurate diagnostic tool currently available, it is reserved solely for prenatal diagnosis of Epidermolysis bullosa, once the family proband has been identified **(Fine, 2008)**.

2.2. CLASSIFICATION OF EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is classified into 4 major types: Epidermolysis bullosa Simplex; Junctional Epidermolysis bullosa, Dystrophic Epidermolysis bullosa and Kindler syndrome (**Pfender *et al,* 2005; *Fine et al*, 2008**).

The four main types of Epidermolysis bullosa are tabulated below (Table 1). There classification is based on:

i. *the level of tissue separation*
ii. *the inheritance pattern and clinical severity*

Table 1: Inherited Epidermolysis Bullosa Types and Subtypes

Epidermolysis bullosa type	Inheritance Pattern	Epidermolysis bullosa subtype	Target protein (gene)	Ultrastructural site of epidermal tissue separation
Epidermolysis bullosa Simplex	Autosomal dominant	Suprabasal	PKP1 (plakophilin-1) DSP (desmoplakin)	Intra-epidermal, within basal keratinocytes
	Autosomal recessive – (X linked)	Basal	KRT5 (Keratin-5) KRT14 (Keratin 14) PLEC1 (plectin) ITGA6, ITGB4 (α6β4 integrin)	
Junctional Epidermolysis bullosa	Autosomal recessive	Herlitz	LAMA3, LAMB3, LAMC2 (laminin-332)	Within the lamina lucida of basement membrane
		Non-Herlitz (Other)	LAMA3, LAMB3, LAMC2, COL17A1 (TYPE XVII collagen) ITGA6, ITGB4 (α6β4 integrin)	
Dystrophic Epidermolysis bullosa	Autosomal recessive	Dominant	COL7A1 (type VII collagen)	Below lamina densa
		Recessive	COL7A1 (type VII collagen)	
Kindler Syndrome	Autosomal recessive		KIND1 (kindling-1)	Mixed cleavage plane

For the purpose of this report, reference will be made to the most common Epidermolysis bullosa subtypes (Epidermolysis bullosa Simplex localized, Epidermolysis bullosa simplex generalized; Dowling-Meara Epidermolysis bullosa simplex; Herlitz and non-Herlitz Junctional Epidermolysis bullosa; dominant Dystrophic Epidermolysis bullosa and recessive Dystrophic Epidermolysis bullosa and Kindler syndrome). For further information, the reader is referred to the thesis delineating Epidermolysis bullosa types in South Africa (**Winship, 1986**).

2.2.1. EPIDERMOLYSIS BULLOSA SIMPLEX

Epidermolysis bullosa Simplex (EBS) is the most common type and denoted as the non-scarring form of the condition. Epidermolysis bullosa Simplex is subdivided into supra-basal and basal forms (**Fine *et al*, 2008**) and is tabulated in Table 2. Ammendments to the classification scheme included the replacement of the Weber Cockayne and Koebner subtypes by localized Epidermolysis bullosa Simplex and Epidermolysis bullosa Simplex generalized respectively.

Mode of inheritance

Epidermolysis bullosa Simplex is usually inherited as autosomal dominant condition, but an autosomal recessive inheritance has been described in some cases (**Pfender *et al*, 2005).**

Mutation in the genes KRT5 or KRT 14, which encode for keratins 5 and 14 are responsible for the dominantly inherited phenotypes of EBS. The skin of the affected person breaks easily because the mutant proteins (keratins) make the inside skeleton of skin cells weak. Blisters arise following separation within the basal keratinocytes and range from mild and localized (in Epidermolysis bullosa Simplex, localized), to mild generalized (in Epidermolysis bullosa Simplex, generalized), to severe (as seen in the Dowling-Meara subtype)(**Pfender *et al*, 2005**). The clinical severity is related to the exact location of point mutations within these keratin polypeptides.

Clinical features (Gorlin *et al,* 2001)

Localized Epidermolysis bullosa Simplex (previously termed Weber-Cockayne subtype), manifests with blisters in friction-exposed sites such as hands and feet. This form of EB is diagnosed in children younger than one year. Despite its limitation to the epidermis and areas of friction, the potential for all skin surfaces to be involved exists because the mutation is inherent within every keratinocyte. Blister formation is exacerbated during the summer months.

Epidermolysis bullosa Simplex superficialis is characterized by blisters, milia, healing with atrophic scarring, nail dystrophy, oral and conjunctival involvement. The oral cavity and corneal surface are the most common extracutaneous sites.

Generalized blistering occurs in Epidermolysis bullosa Simplex generalized and the Dowling-Meara herpetiformis subtype. In the former, blisters arise not only in response to friction or trauma, but also due to a predisposition to heat. Unlike the localized variant, these blisters are evident from birth, or during the first few weeks of life. The involved sites include the feet, hands and neck, with infrequent extra-cutaneous involvement. Lesions do not heal with scarring or pigmentation and generally improves by puberty. Occasional intra-oral blister formation occurs, with no associated tooth alterations, but not as prominently as in the more severe subtypes.

The Dowling-Meara herpetiformis subtype may be evident at birth or within the first three months, manifesting with widespread blistering, erythema and skin loss. A hoarse cry is characteristic and the characteristic herpetiform bullae arrangement may only become evident later in life. These serous hemorrhagic blisters occur on any part of the body, especially the palms, soles, peri-oral regions, trunk and neck. Lesions usually heal without scarring but a concomitant intense inflammatory reaction within the hemorrhagic blisters is elicited. Associated milia and pigmentary alterations of the skin are reported. The skin lesions improve during periods of fever, in the summer months, and with advancing age. The clinical picture is equally variable within and between families.

Epidermolysis bullosa Simplex with muscular dystrophy (Epidermolysis bullosa simplex-MD) has an autosomal recessive inheritance pattern and is the most severe Epidermolysis bullosa Simplex subtype (**Gorlin *et al* 2001**, **Uitto and Richard, 2005**). Its onset is evident at birth, manifesting with erythema, widespread blistering, erosions and denuded skin. These features become more widespread and severe with increasing age involving the extremities, with frequent oral and other mucosal involvement. Other sequential features include palmoplantar keratoderma, nail dystrophy, milia, pigmentary changes and secondary infections. Healing by mild atrophic scarring occurs in most persons. Mutations in the *plectin* gene implicated in Epidermolysis bullosa simplex-MD could account for the skin fragility and muscular weakness seen in these persons. Its hypothesized that plectin plays a role in muscle facilitating binding of actin to membrane complexes.

Table 2: Revised Epidermolysis bullosa Simplex (EBS) Classification

Major Epidermolysis bullosa Simplex types	Epidermolysis bullosa Simplex subtypes	Target proteins
Suprabasal	Lethal acantholytic epidermolysis bullosa	Desmoplakin
	Plakophilin deficiency	Plakophilin
	Epidermolysis bullosas superficialis (E BSS)	?
Basal	Epidermolysis bullosa simplex, localized (EBS-LOC) *	K5, K14
	Epidermolysis bullosa simplex Dowling Meara (EBS-DM)	K5, K14
	Epidermolysis bullosa simplex , other generalized (EBS, gen- nonDM) #	K5, K14
	Epidermolysis bullosa simplex with mottled pigmentation (EBS-MP)	K5
	Epidermolysis bullosa simplex with muscular dystrophy (EBS-MD)	Plectin
	Epidermolysis bullosa simplex with pyloric atresia (EBS-PA)	Plectin,α6β4 integrin
	Epidermolysis bullosa simplex, autosomal recessive (EBS-AR)	K14
	Epidermolysis bullosa simplex, Ogna (EBS-Og)	Plectin
	Epidermolysis bullosa simplex migratory circinate (EBS-migr)	K5

*Epidermolysis bullosa simplex, localized was previously denoted Weber-Cockayne

#Epidermolysis bullosa simplex generalized includes patients previously classified as Epidermolysis bullosa simplex Koebner subtype.

2.2.2. JUNCTIONAL EPIDERMOLYSIS BULLOSA (JEB)

Junctional Epidermolysis bullosa is divided into 2 major and several minor groups based on clinical severity (**Fine *et al*, 2008**). The two major variants include Herlitz and non-Herlitz types and the distinction is based upon disease severity. In the Herlitz subtype, the pathology occurs at the level of the lamina lucida. In the non-Herlitz subtype, blister formation occurs within the basement membrane zone at the hemi-desmosomal or the basal cell/lamina lucida interface. In general, mild blistering occurs in the non-Herlitz variant and the Herlitz sub-type manifests with a more severe phenotype, with persons generally not surviving beyond infancy (**Uitto and Richard, 2005).**

Mode of transmission

Junctional Epidermolysis bullosa has an almost exclusively autosomal recessive form of inheritance, with mutations in four genes encoding the affected proteins. These include subunits of laminin 332 complex: alpha 3 (LAMA 3); beta-3 (LAMB3) and gamma-2 (LAMC2). Laminins are essential components of anchoring filaments in the basement membrane zone. In addition, mutations of Type XVII collagen and α6β4 integrin are associated with non-Herlitz forms such as Junctional Epidermolysis bullosa with pyloric atresia).

Clinical features

The non-Herlitz Junctional Epidermolysis bullosa is subdivided into 2 distinct groups (Table 3) – Junctional Epidermolysis bullosa non-Herlitz generalized and localized. In this subtype, affected persons survive infancy and live a normal lifespan, with the disease process slowing with age. Junctional Epidermolysis bullosa non-Herlitz generalized is characterized by blister formation in addition to extra-cutaneous manifestations: fingernail dystrophy, focal scarring alopecia of the scalp, loss of eyelashes, dental anomalies (enamel hypoplasia, pitting of the enamel) and patchy macular hyperpigmentation (**Uitto and Richard, 2005**). The same clinical features occur in Junctional Epidermolysis bullosa Herlitz subtype, but with increased severity. Clinically,

phenotypic variations occur within families and the condition is non-lethal, with no genotype/phenotype correlation.

The Herlitz junctional Epidermolysis bullosa subtype has more severe manifestations, often with fatal consequences, being mostly due to respiratory failure and sepsis. Persons with Herlitz junctional Epidermolysis bullosa have hemidesmosomal hypoplasia with a mild decrease in tonofibrils. This form exhibits exuberant granulation tissue formation following erosions and blister formation, most notably around or within body orifices (peri-oral, perinasal, intranasal and infraocular), axilla, uppermost back and posterior neck (**Pfender *et al,* 2005; Fine *et al,* 2008).** Blisters involve the entire skin surface and multiple organ involvement is common. Oral involvement is common and will be discussed in **Section 2.3.**

Anemia, growth retardation and gingiva-laryngeal strictures are common to both Junctional Epidermolysis bullosa subtypes.

Table 3: Junctional Epidermolysis bullosa subtypes

Major Junctional Epidermolysis bullosa type	Subtype	Targeted protein
Junctional Epidermolysis bullosa, Herlitz (JEB-H)		Laminin 332
Junctional Epidermolysis bullosa other (JEB-O)	Junctional Epidermolysis bullosa, non-Herlitz generalized (JEB-nHgen) [#]	Laminin 332, type XVII collagen
	Junctional Epidermolysis bullosa, non-Herlitz localized (JEB-Nh loc)	Type XVII collagen
	Junctional Epidermolysis bullosa with pyloric atresia (JE B-PA)	α6β4 integrin
	Junctional Epidermolysis bullosa, inverse (JEB-I)	Laminin 332
	Junctional Epidermolysis bullosa, late onset (JEB-lo) [+]	**?**
	LOC Syndrome	Laminin 332

[#] Junctional Epidermolysis bullosa, non-Herlitz generalized is formerly known as generalized atrophic benign (GAB Epidermolysis bullosa)

[+] Junctional Epidermolysis bullosa late onset was formerly known as junctional Epidermolysis bullosa progressive

2.2.3. DYSTROPHIC EPIDERMOLYSIS BULLOSA

Persons with Dystrophic Epidermolysis bullosa exhibit a broad range of phenotypes. This variant is generally associated with extensive scarring because of the biologic location of the defect and blistering is induced by minimal friction (**Pfender *et al*, 2005**).

Mode of transmission

Dystrophic Epidermolysis bullosa may have either an autosomal dominant or recessive inheritance pattern. In Dystrophic Epidermolysis bullosa, mutations occur in COL_7A_I gene that encodes type VII collagen. The latter forms the predominant component of the anchoring fibrils that connect the basement membrane to the underlying dermis. Mutations in the gene, located at 3q21.1 results in an abnormal morphology, reduction or complete absence of these anchoring fibrils at the dermal-epidermal junction (**Pfender *et al*, 2005; Uitto and Richard, 2005; Azrak *et al*, 2006**). In addition, the mutation also results in increased collagen disintegration within the superficial dermis due to excess collagenase synthesis.

Clinical manifestations

Clinically Dystrophic Epidermolysis bullosa lesions range from mild (in the dominant variant) to severe and mutilating (in the autosomal recessive Hallopeau-Siemens subtype). In the milder form, blistering of the skin and mucous membranes forms in response to mechanical force, due to a shortage of anchoring fibrils in the sub-basal lamina region. Clinically flat, pink, scar-producing bullae are seen on the ankles, knees, hands, elbows and feet, in decreasing order or frequency. Milia occur less commonly than with the recessive variants and the nails are usually thick and dystrophic. The cornea and conjunctiva are never involved, unlike recessive dystrophic cases. About 20% of persons manifest clinical changes before the age of 1 year and lesions generally improve with age (**Fine *et al*, 1989 and 2008**).

The autosomal recessive Dystrophic Epidermolysis bullosa subtype (RDEBg or the Hallopeau-Siemens variant) involves all extremities, joints and mucosal surfaces, with eye and oral involvement being most common. Bullae usually arise at or shortly after birth, at sites predisposed to minor pressure, trauma or even spontaneously. Initially the fluid contained within the bullae is sterile, but it may become secondarily infected and haemorrhagic. Ruptured bullae reveal a raw painful surface and healing elicits keloidal disfiguring scars and skin contractures as well as continuous morbid fibrous adhesions of the mucosa (**Horn and Tidman, 2002; Fine *et al*, 2008)**.

The metacarpals become slender, overconstricted and distal phalanges become pointed and claw-like. Scarring of the hand leads to mitten deformities, pseudosyndactaly, dystrophy and contractures and nails are often absent or dystrophic (**Gorlin *et al*, 2001**).

Mucosal involvement can eventually cause complications involving the oesophagus, intestinal and urinary tracts. The upper half of the oesophagus may become sequentially stenotic in childhood, with subsequent dysphagia. The resultant nutritional difficulties retard growth with subsequent shortened life spans. Anemia is a common presentation due to bleeding from the denuded areas.

Squamous cell carcinomas are common and by the age of 25 and 35 years, 23.7% and 51%, patients with Hallopeau-Siemens variants have developed at least one squamous cell carcinoma. In addition, the cumulative risk of malignant melanoma was reported as being 4.1% by age 12 years.

Little increased risk of death occurs in recessive Dystrophic Epidermolysis bullosa patients until after the age of 20. By age 40, however the risk of death is 33.3% coinciding with the timing of consequent reports of squamous cell carcinomas in this patient population.

A rare and less severe variant of autosomal recessive dystrophic Epidermolysis bullosa is RDEB inverse. It is clinically characterized by lesions located in flexural areas of the body sparing the fingers and toes, but without the severe generalized blistering, growth retardation and digital webbing characteristic of Hallopeau-Siemens dystrophic Epidermolyis bullosa variant. Oral involvement is similar to, but milder than the Hallopeau-Siemens subtype. These include ankyloglossia, loss of tongue papillae, and obliteration of the oral vestibule between the lips and gingival, with apparently normal teeth (**Wright *et al*, 1993).**

Table 4: Major Dystrophic Epidermolysis bullosa types

Dystrophic Epidermolysis bullosa types	Subtypes	Targeted protein
Dystrophic EB	Dystrophic Epidermolysis bullosa, generalized (DEB-gen)	Type VII collagen
	Dystrophic Epidermolysis bullosa, acral (DEB-ac)	
	Dystrophic Epidermolysis bullosa, pretibial (DEB-Pt)	
	Dystrophic Epidermolysis pruriginosa (DEB-Pr)	
	Dystrophic Epidermolysis bullosa, nails only (DEB-na)	
	Dystrophic Epidermolysis bullosa, bullous dermolysis of the newborn (DEB-BDN)	
Recessive dystrophic EB	Recessive Epidermolysis bullosa, severe generalized (RDEB-sev gen)	Type VII collagen
	Recessive Epidermolysis bullosa, generalized other (RDEB-O)	
	Recessive Epidermolysis bullosa, generalized other, inverse (RDEB-I) Recessive Epidermolysis bullosa, generalized other Recessive dystrophic Epidermolysis bullosa pretibial (RDEB-Pt) Recessive dystrophic Epidermolysis bullosa pruriginosa (RDEB-Pr) Recessive Epidermolysis bullosa, generalized, centripitalis (RDEB-Ce) Recessive Epidermolysis bullosa, generalized, bullous dermolysis of the newborn (RDEB-BDN)	

RDEB, severe generalized was previously known as RDEB, Hallopeau-Siemens.

2.2.4. KINDLER SYNDROME

Kindler syndrome is and autosomal recessive genodermatosis characterized by trauma-induced blistering, poikiloderma, skin atrophy, mucosal inflammation and photosensitivity (**Lai-Cheong *et al,* 2009**). Despite the inclusion of Kindler syndrome as a fourth subtype in the revised Epidermolysis bullosa classification system (**Fine *et al,* 2008**), it has distinct clinical, pathologic and molecular abnormalities.

In Kindler syndrome, desmosomal and hemidesmosomal mutations are not implicated. A defect or deficiency in the focal adhesion protein (fermitin family homologue), results in an abnormality of the association between the actin cytoskeleton of the extracellular matrix. Clinically it resembles Dystrophic Epidermolysis bullosa and congenital poikiloderma, but features diversify with increasing age. Congenital poikiloderma is an inherited autosomal recessive syndrome seen chiefly in women. Manifestations include reticular, atrophic, hyperpigmented and telangiectatic cutaneous plaques, often with associated juvenile cataracts, a saddle nose, congenital bone defects, hypogonadism, with differential growth of hair, nails and teeth (**Chimenos *et al,* 2003; Lai-Cheong *et al,* 2009**).

Clinical features of Kindler syndrome

The clinical features of this syndrome include blistering of trauma-exposed sites, progressive poikiloderma, atrophy of the skin on the dorsum of the hands and feet and photosensitivity. Both the blistering and photosensitivity becomes less evident with age.

Early-onset periodontal disease and severe desquamative gingivitis causes bleeding gums and tooth loss. Mucosal involvement leads to anal, vaginal, urethral and oesophageal stenosis. Gastro-intestinal tract involvement manifests with bloody gingiva and severe colitis, while finger webbing, pseudosyndactaly, squamous cell carcinoma and nail dystrophy are also reported (**Chimenos *et al,* 2003**).

Diagnosis of KS

The genetic defect is unknown and ultrastructural analysis via TEM is often non-specific, with variability in affected persons. The purported ultrastructural defects are numerous. Some studies have suggested a defect in the adhesion molecules anchoring the basal cell layer to the lamina densa, others noted vacuolization of the basal layer and epidermal atrophy (**cited in Wiebe *et al*, 2008)**, multiple cleavage planes, prominent reduplication of the lamina densa, with cleft development in regions following destruction of the lamina densa. Anchoring fibrils and hemidesmosomes may still be intact. Electron microscopy of blistered KS skin reveals cleft formation within the basal keratinocytes, below the lamina densa, or within the lamina lucida. In addition, tonofilament clumping is evident in keratinocytes next to blistered areas – similar to some Epidermolysis bullosa cases. Two pathognomonic features of Kindler syndrome includes: reduplication of lamina densa and disorganization of basal cell layer. Features of other poikilodermas are also consistently found within such biopsies. These include melanin incontinence (seen within the dermis), along with the presence of melanophages, colloid bodies and ectasia of blood vessels. In addition, collagen lysis with disruption of elastic tissues may be seen.

Ultrastructural analysis is location dependant, with cleavage planes close to the dermal-epidermal junction in a skin biopsy from a blistered area. A skin biopsy of an area with poikiloderma exhibits hyperkeratosis and epidermal atrophy with loss of rete ridges.

2.3. ORAL MANIFESTATIONS OF EPIDERMOLYSIS BULLOSA

Oral manifestations of Epidermolysis bullosa are variable, ranging from small vesicles to large bullae that rupture to reveal a denuded surface (**Travis *et al,* 1992**). Such severe dental and gingival anomalies occur commonly in persons with recessive Dystrophic Epidermolysis bullosa (**Silva *et al,* 2004**). These occur on virtually any intra-oral surface and may be present at birth due to the intra-uterine activity of fetal sucking in persons with recessive dystrophic Epidermolysis bullosa (**Azrak *et al,* 2006**). Table 5 summarizes the oral findings documented in case reports of persons with Epidermolysis bullosa (**Tomlinson, 1983; Serrano-Martinez *et al,* 2003; Silva *et al,* 2004; Azrak *et al,* 2006; Pekinar *et al,* 2007; Pacheco *et al,* 2008; Siqueira *et al* , 2008**).

2.3.1. Oral manifestations in Epidermolysis bullosa Simplex (Gorlin *et al,* 2001)

There is a paucity of information regarding oral manifestations seen in the Epidermolysis bullosa Simplex type. Some authors have reported on increased caries susceptibility in hypoplastic enamel, delayed eruption, frequent retention, with little information regarding lesion frequency. There is consensus that no correlation exists between the cutaneous involvement and degree of dental involvement. Histologic studies of unerupted teeth published by Delaire and colleagues and Arwill and co-workers noted enamel hypoplasia with absence of prismatic structures. Examination of extracted teeth showed an accentuation of enamel tuft formation extending from the dentino-enamel junction to the enamel surface. Irregular dentinal gingiva and indentations were at the dentino-enamel junction.

Oral mucosal involvement can occur in both the localized and generalized Epidermolysis bullosa simplex subtypes. These blisters generally do not pose a problem during feeding except in the Dowling-Meara herpetiformis subtype. Some infants with this subtype can manifest with severe blistering of the mouth and oesophagus, making it difficult for the baby to feed. The application of teething gels prior to feeding as well as moistening of the teat with cooled boiled water before feeding will prevent the dry teat sticking to the

blistered areas. In addition moistening the lips with petroleum jelly can prevent further damage.

2.3.2. Oral manifestations in Junctional Epidermolysis bullosa (**Almaani *et al*, 2008**).:

Oral lesions vary according to the subtype. Bullae and chronic erosions are found in nearly all patients especially at the junction of the hard and soft palates. These bullae are remarkably fragile and hemorrhagic. Oral ulcers and blisters are seen at birth or shortly thereafter. Enamel hypoplasia and pitting of the molars occurs. Enamel formation is abnormal, leading to extensive caries. Histological studies of soft tissue lesions show cleavage between the epithelium and the connective tissue. Peri-oral and peri-nasal crusted and granular hemorrhagic lesions tend to develop between the sixth and twelfth months of life. These lesions are considered pathognomonic for the Herlitz type of Epidermolysis bullosa in older patients.

2.3.2 Oral manifestations associated with Dystrophic Epidermolysis bullosa

The most prevalent oral mucosal involvement is seen in recessive Dystrophic Epidermolysis bullosa with generalized involvement (**Serrano-Martinez *et al*, 2003; Abercrombie *et al*, 2008**). These include blisters, malformed teeth, hypoplastic enamel and extensive dental caries. Repeated vesicles, bullae and erosions result in scar formation, which consequential intra-oral alterations: atrophy of tongue papillae and palatal folds; obliteration of the gingival vestibule and frenum; tonsillar pillar fusion, ankyloglossia and microstomia.

The extensive dental caries seen in these persons is hypothesized to be due to a soft diet rich in carbohydrates. The soft tissue blistering and associated discomfort is responsible for this limited diet. In addition, reduced oral clearance because of limited tongue mobility and vestibular constriction may also play a role, but no evidence of reduced salivary function was found.

In dystrophic Epidermolysis bullosa, bullous eruptions form after trauma and heal leaving atrophic scars and milia. These are epidermoid cysts originating from detached islands of epithelium in sites of previous bullae and appear as small white nodules beneath the scars. Teeth are generally unaffected and whilst a 20% prevalence of oral bullae has been reported, however the samples have been small.

Oral mucosal blisters can occur at any intra-oral site and contain either sterile fluid or blood, with the lingual mucosa being the most frequent location, followed by the soft and hard palate (**Serrano-Martinez *et al,* 2003).** They are painful and heal by fibrosis. The mucosa and attached gingiva is smooth, erythematous and oedematous. Fetal sucking in the uterus can elicit blisters that are noticeable at birth. The consequential healing and scarring will over time result in microstomia (decreased oral aperture); tongue atrophy and lingual depapillation; ankyloglossia; atrophy of the palatal folds; gingival ridge obliteration, tonsillar pillar fusion, ankyloglossia and microstomia. Dysfunction of the opening of the pharynx may result in stricture of the air passage and digestive system. Thus maintaining their dentition not only reduces the risk of oral and oesophageal mucosal trauma, but also results in improved nutrition (**Penarrocha *et al,* 2007**). During blister formation and cicatrization, milium cysts develop due to entrapment of epithelial cells (**Serrano-Martinez *et al,* 2003**). This occurs often in the hard palate.

A reduced enamel mineral content was reported in severe forms of Dystrophic Epidermolysis bullosa, but developmental enamel defects were only reported in 8.6% of persons in this prevalence study (**Wright, 1993)**. Caries is quite prevalent because of the reduced oral hygiene and consumption of soft foods (**Azrak *et al,* 2006**).

Wright and Fine, 1994 reported areas of leukoplakia and oral squamous cell carcinoma of the lingual mucosa, suggested being due to repeated ulceration and re-epithelialization and periodic assessment is recommended for recessive Dystrophic Epidermolysis bullosa persons (**Serrano-Martinez *et al,* 2003)**.

2.3.3 Oral Manifestations of Kindler Syndrome

Few reports of Kindler Syndrome as well as its management are documented in the literature. Oral findings such as gingivitis, bleeding gums, mucosal erosions, atrophy, white patches, periodontal disease **(Wiebe *et al,* 2008)**, lip pigmentation and limited mouth opening have been reported. The latter is due to sclerosis at the commissures of the mouth following healing of bulla and resultant scar formation **(Rickets *et al,* 1997)**.

Desquamative gingivitis seen may resemble that seen in other vesiculobullous conditions such as pemphigus, lichen planus or pemphigoid. In Kindler syndrome, the marginal gingiva is desquamative, inflamed and erythematous because of increased susceptibility to inflammation induced by bacterial plaque in this fragile gingival. Inadequate oral hygiene is a common finding due to a combination of oral discomfort and reduced dexterity. To this end, regular oral hygiene maintenance visits for scaling and polishing has shown to significantly improve both the gingival condition as well as patient comfort **(Wiebe *et al*, 2008).**

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2.4. ORAL HEALTH-RELATED QUALITY OF LIFE MEASURES (OHRQoL)

"*The extension of people's lifespans and the enhancement of their quality of life*" form pivotal goals of health-care systems (**Slade *et al,* 1998**). There has been a concerted paradigm shift with regard to the perception and evaluation of oral health. Oral health does not only imply being disease free, but also an improvement in the quality of health (**Allen, 2007**). Previous oral health assessment involved the measurement of disease, by virtue of various clinical indices (**Guyatt *et al,* 1993**). These measures however focus on disease outcome, only reflecting the end- point of disease, with no indication as to the patient's perspective on how it affects their daily functioning (**Allen, 2003**). Implicit herein is that while clinical indicators are vital for oral disease measurement, when used alone, proves inadequate for a true oral health assessment and formulation of treatment needs. This assessment must measure how oral conditions interfere with everyday life and if they alter normal conduct such as inability to go to work or school.

The term oral health related quality of life (OHR-QOL) is defined as "a broad conception of health, encompassing the traditional definition of health, but also including individuals' subjective impact of health on well-being and functioning in every-day life" **(cited in Allen, 2007**). In 1989, Locker provided the impetus for a more "holistic" model of health measurement based on the WHO classification of impairment, disabilities and handicap (**Allen, 2003**). Implicit in this model is that disease, health and quality of life be separately defined. This became apparent in studies of chronic conditions who reported a good quality of life, despite severe physical limitations (**Allen, 2007**). Thus, health and quality of life are both theoretically and philosophically distinct concepts and in addition, so too are measures of health status and those assessing oral health-related quality of life are distinct **(Allen, 2007).** In a critical review of such measures, two researchers highlighted criteria, which must be met for measures used to assess "health related quality of life", but others felt that their criteria were too rigorous and suggested a more liberal approach. Despite their differences, it was concluded that two pertinent issues, common to both approaches, must be considered when evaluating such measures. Firstly, the measure must represent patients' perspectives and concerns

rather than those of medical practitioners. Secondly, these measures must integrate everyday- life activities important to the target group (**Allen, 2007**).

Various instruments for the assessment of oral-health related quality of life (OHRQoL) measures have evolved and been described and explored in studies (**Allen, 2003 and 2007**). These include the Geriatric/General Oral Health Index of Assessment (GOHAI); Oral Health Impact Profile (OHIP); Oral Impacts on Daily Performance (OIDP) and the Child Oral Health Quality of Life Questionnaires. Locker and Allen, (2007), critically appraised the validity and reliability of these OHRQoL measures and compared them to the ideal characteristics of oral-health related quality of life measure, as developed by Adulyanon and Sheiham, 1997. They concluded that the Geriatric/General Oral Health Index of Assessment (GOHIA) measure met too few requirements and was best reserved for subjective assessment of oral health status. While the OHIP assesses self-perceived oral health and measure the social impact of oral disorders, its disadvantage was that, the measures were "expert-centered", designed to fit a theoretical framework rather than reflect the importance to the persons from whom they were obtained. The Oral Impacts on Daily Performances measure was unique in that its design enabled assessment of the population's dental needs, in collaboration with conventional measures. Secondly, it is the "gold standard" measurement for assessing "behavioural" effects of oral disorders and the degree to which the ability to perform physical, psychological and social performances is compromised". Despite the fact that it appears to be the most "expert-centred" measure, it has the most compound item scoring system. It assesses both impact frequency and severity (**Bernabe *et al,* 2007**), such that multiplying these parameters gives one specific performance scores (highlighting specific dental conditions that resulted in the impact). Adding the scores gives one a total impact score. Linking the specific oral problem to the impact may be useful in assessing dental health needs as well as prioritizing dental health care services – ensuring that the problem associated with the impact receives treatment (**Gherupong *et al,* 2004**).

Oral health related quality of life

Epidermolysis bullosa is a chronic condition for which there is no curative therapy. Treatment is palliative and is aimed at improving patient comfort. The medical and psychological aspects of Epidermolysis bullosa are well documented. Thus, the rationale for assessing oral impacts in this population is warranted, because oral disease does affect eating, smiling and socializing. OHRQoL measures have largely been used to assess impacts in population-based settings, with limited exposure in specific patient based cohorts (**Bernabe *et al,* 2007**). The nature of reports on oral manifestations in persons with Epidermolysis bullosa is largely case reports and the need to assess the sensitivity of an OHRQoL measure such an OIDP was investigated.

Oral Impact on Daily Performance (OIDP) Tool:

The oral impact on daily performance measure (OIDP) is the most widely used quality of life assessment socio-dental indicator. The conceptual framework is based upon the WHO's International Classification of Impairments, Disabilities and Handicaps. The OIDP has been suitably modified to encompass varying degrees of the concept: oral status or impairments, intermediate impacts (pain, discomfort, functional limitation or dissatisfaction with appearance), and ultimate impacts which cover the concepts of disability and handicap. The concept of the (OIDP) focuses on the third measurement level by assessing the frequency, severity and extent to which oral disease impact on the participants' ability to fulfill eight daily tasks. These include eating and enjoyment thereof; speaking and clear pronunciation; cleaning teeth; sleeping and relaxation; smiling, laughing and showing teeth without fear of embarrassment; maintaining one's emotional state without becoming irritable; the ability to perform usual work or social role and enjoying contact with others.

Frequency and severity estimates in all participants are calculated using five point scales. The responses to the frequency impact ranges from 0 (not affected in the past six months) to 5 (everyday or nearly everyday for the past 6 months). Impact severity scores are rated by participants on a scale of 0 (no effect) to 5 (severe). Each performance score is calculated by multiplying the frequency and severity scores extracted from the relevant

questions. The overall performance score involves addition of each performance score, as described below:

Performance score = Frequency score*Severity score
(E.g. Eating score = Eating Frequency*Eating Severity)

OIDP score = [(eating frequency*eating severity) + (speaking frequency*speaking severity) + (cleaning frequency*cleaning severity) + (sleeping frequency*sleeping severity) + (smiling frequency*smiling severity) + (emotional frequency*emotional severity) + (work/schoolwork frequency*work/schoolwork severity) + (social contact frequency*social contact severity)]*100/200

The OIDP is validated for use in both adults and children between the ages of 11-12 year old (**Tsakos *et al*, 2001; Bernabe *et al*, 2007;**). The use of the OIDP in children younger than 11 years old was adapted for the present study. A systematic review undertaken to determine the correlation between parents' and their childrens' rating of "ill-health" on the children's lives (**Barbosa, 2007**), concluded that the parent's responses were considered representative.

CHAPTER 3: METHODOLOGY

3.1. AIM

To assess the prevalence and impact of oral lesions on daily activities (OIDP) in persons with Epidermolysis bullosa in Cape Town, South Africa.

3.2. OBJECTIVES

1. To determine the prevalence of oral mucosal lesions
2. To determine the dental caries experience (DMF and dmf)
3. To assess the impact of frequency, severity and extent (number of affected daily activities) of oral lesions on daily activities

CHAPTER 4: RESEARCH DESIGN AND METHODOLOGY

This chapter discusses the research design and methodology used in the study and describes the research tool and data collection method.

4.1. Study Design

This present study is a case-controlled, descriptive analysis of the way in which perceived oral lesions impact on the quality of life in persons with Epidermolysis bullosa. The latter was assessed by conducting face-to-face interviews using a structured questionnaire.

4.2. Selection of study population

The study population consisted of fourteen persons with a confirmed diagnosis of hereditary Epidermolysis bullosa attending the dermatology clinics at the Red Cross and Groote Schuur hospitals and 18 persons loosely matched for age, gender, socio-economic and dental status (control group). Three Epidermolysis bullosa persons were not available for evaluation. The chosen sites were dedicated clinics where persons with Epidermolysis bullosa presented for regular follow-up visits. Social status amongst the participants considered "equal" as both Epidermolysis bullosa and control persons utilized the public health facilities. The participants were divided into three groups: "toddlers"(< 5years of age); "older children"(5 -14 years) and "adults"(15 years and older).

4.3. Study population and sampling

The sampling of the participants from the clinics was by means of a convenience sample of **all** available Epidermolysis bullosa persons attending the Red Cross Children's hospital and Groote Schuur dermatology clinics, with a loosely matched control group of persons attending the same dermatology clinics.

4.3.1. Inclusion criteria

Persons with Epidermolysis bullosa

- Persons with a confirmed diagnosis of Epidermolysis bullosa

- All ages
- Fully informed , written consent obtained
- Permission obtained for clinical photography and for publication of data and photographs.

Control Group

- Persons loosely matched for age; dental status (primary dentition; mixed dentition; secondary dentition); attending the dermatology clinic at the aforementioned hospitals
- Fully informed, written consent obtained
- Permission obtained for clinical photography and for publication of data and photographs

4.4 Ethical approval

Ethical approval was obtained from the University of the Western Cape Dental Faculty and The University of Cape Town Ethical Review Board. Individual patient consent for the clinical oral examination and the face-to-face interview responses were recorded on the questionnaire. Participants were free to withdraw from the study at any stage and assured that this would not affect any referral for treatment. Participants received information about their oral health status following the examination.

4.5. Data Collection

The parameters assessed included demographic measurements; presence of oral lesions; dental caries index (dmf and DMF)*; gingival inflammation (GI); plaque status (PI) and OHRQoL data.

* As described in the World Health Organization Oral Health Survey Manual (1997)

1.Demographic data

This included age at last birthday; gender; occupational status and reason for attending the dermatology clinic.

2. Oral lesions

The presence of oral and peri-oral lesions was recorded on data capturing sheets.

3.Dental caries index

The dental caries index measured the dental caries experience of the participants. The indices used were DMF and dmf (**Klein *et al,* 1938 in WHO, 1997**).

3.i. DMF index measured the condition of the permanent teeth:

D =decayed teeth

M =missing teeth (due to caries)

F = filled teeth (with amalgam and or composite material)

Procedure

Each tooth in the mouth was examined using set criteria and teeth are classified as decayed, missing, filled or sound. The sum of decayed, missing and filled gave the individual DMF.

3.ii. dmf

This index is applicable to children identify primary teeth in children 5 years and under and is recorded similarly to DMF for permanent teeth:

d = decayed teeth

m = missing teeth

f = filled teeth

Each tooth in the mouth was examined using set criteria and teeth are classified as decayed, missing, filled or sound. The sum of decayed, missing and filled gave the individual dmf.

4. *Plaque Index* **(Silness and Löe, 1964 – in Katzenellenbogen *et al*, 1997*)***

The plaque index (PI) assessed the amount of plaque present at the gingival area. The selected teeth were examined on four gingival areas (distal, mesial, facial and lingual). Each area was assigned a score from 0-3.

The plaque index was scored as follows:

Score 0 : No plaque

Score 1 : A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque is visible after application of disclosing solution or by using the probe on the tooth surface

Score 2 : Moderate accumulation of soft deposits within the gingival pocket, or on the tooth and gingival margin, which can be seen with the naked eye.

Score 3: Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

5. Gingival Index ***(*Löe and Silness, 1963 – in Katzenellenbogen *et al*, 1997***)

The Gingival Index (GI) assessed the degree of gingival inflammation present in the distal, mesial, facial and lingual areas. Each area was assigned a score from 0-3.

The Gingival Index was recorded as follows:

Score 0: Absence of inflammation

Score 1: Mild inflammation; slight change in colour and little change in texture.

Score 2: Moderate inflammation; moderate glazing; redness; edema and hypertrophy; bleeding on pressure

Score 3: Severe inflammation; marked redness and hypertrophy; tendency towards spontaneous bleeding

6. Oral Impacts on Daily Performance (OIDP)

OHRQoL was assessed via a structured individual interview approach that recorded OIDP data in addition to two global self-report indicators (perceived general and oral health problems and perceived oral treatment need).

The use of global health oral ratings have been extensively employed and found to correlate with functional impairment and well-being (**Robinson *et al,* 2001**).Participants were asked to rate their general health and perceived satisfaction with their mouth (oral health) on a scale of 0 (poor) to 5 (excellent). Due to the small sample size, variables for the perception of general and dental health were collated into two groups: "poor or fair" (scores 1-2) and "good, very good, excellent" (scores 3-5). The perceived need for dental treatment was categorized into "no-not much need" (scores of 1-2) and "need" (scores of 3-5). All interviews were conducted by the principle researcher.

4.5. Data analysis

Simple frequency counts of oral lesions were captured in Microsoft Excel® and analyzed with the same package. The more complex statistical calculations were performed using Number Cruncher Statistical System (NCSS ®). Data for the OIDP tool was obtained from the questionnaires. The data was coded and entered into the computer and analyzed based on the points assigned to each question. This was to determine associations between perceived oral conditions and its impact on eight daily activities in the participants. Non-parametric tests were used due to a lack of normality (standard statistical distribution) and the small sample sizes involved. The Kruskal –Wallis non-parametric test compared the Medians (location) of several independent groups.

Various graphical methods were used to display the results obtained from the data collection, such as Pie charts, Violin plots as well as Box plots. The violin plot is a density plot showing the relative concentrations of observations of a univariate measurement, which enables the reader to distinguish more than one mode if present. A

Box plot does not have the ability to identify the presence of more than one mode in an empirical distribution.

CHAPTER 5: RESULTS

5.1 Introduction

This section details the findings of this study. Participants provided demographic information regarding their age, sex and occupational status. Records pertaining to their Epidermolysis diagnosis, reason for visiting the dermatology clinic (in control group) and medicaments used were obtained from the participants' medical files. Face-to-face individual interviews were used to obtain the data relating to global oral health rating and the OIDP tool.

5.2 Demography of the study population

Thirty-two participants (32) were included in the study and comprised fourteen Epidermolysis bullosa (14) and eighteen control persons (18), loosely matched for gender, age, socio-economic and dental status.

1. Gender distribution

Half the sample was female with an equal distribution in both the Epidermolysis bullosa (8) and control group (8). There were ten and six males in the control and Epidermolysis bullosa groups respectively.

2. Age range

The age distribution of the sample (Table 6) was broad and ranged from 1 to 55 years in the control group and from 2 to 53 years in the Epidermolysis bullosa group.

Table 6: Age and gender distribution in Epidermolysis bullosa and control participants

Data	Control		Epidermolysis bullosa	
	Female	Male	Female	Male
Total sample number	8	10	8	6
Average age in years	20.25	20.20	21.88	19.00
Standard Deviation	13.25	19.33	17.31	14.25
Min of age in years	1	2	2	3
Max of age in years	36	55	53	36

3. Occupational status

The occupational status of the two groups was similar (Table 7), except that the two unemployed persons with Epidermolysis bullosa received disability grants as a source of income.

Table 7: Occupational status of sample

	Epidermolysis bullosa (14)	Control (18)
Pre-school	3	3
Scholar	5	7
Unemployed	2	2
Employed	4	6

4. Reason for attending the dermatology clinic (Figure 1)

Epidermolysis bullosa Simplex (Figure 2) was the most common type, seen in 9 of the fourteen Epidermolysis bullosa participants. Two persons had Junctional EB , two others had Dystrophic EB (Figures 3,4) and one person had Kindler syndrome (Figure 5).

Amongst the control participants, most children presented for eczema and asthma related problems (Table 8). The adults in the control group had a broad range of presentations, ranging from seborrheic keratosis to erythema multiforme and basal cell carcinoma.

Figure 1: Epidermolysis bullosa types present in the sample

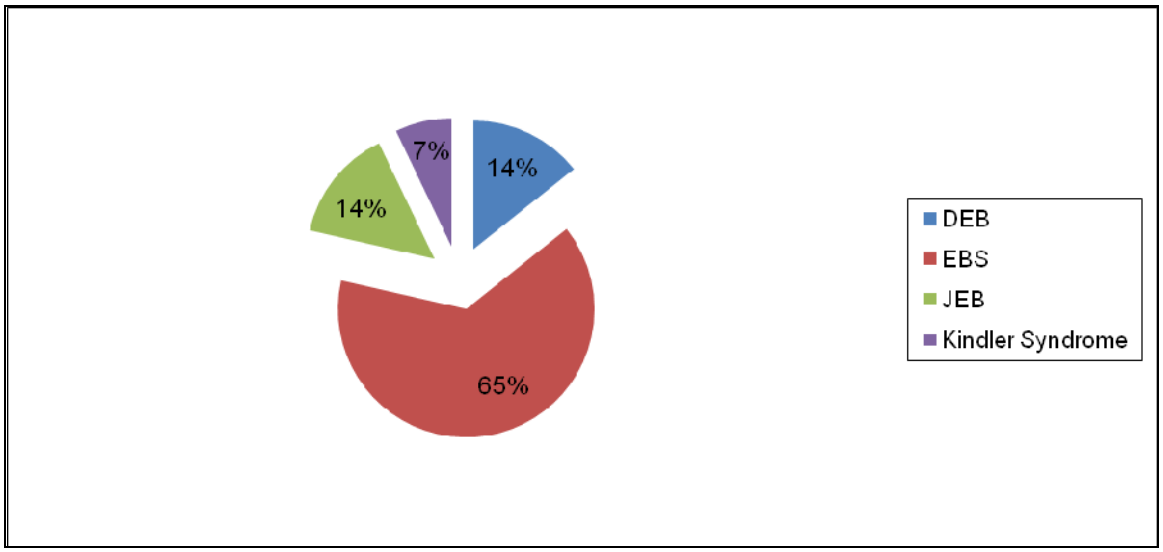


Table 8: Reason for attending the dermatology clinic in control participants

	Gender	
	Female	**Male**
Swollen adenoids	-	1
Asthma	1	1
Basal cell carcinoma	-	1
Control	1	-
Eczema	-	4
Erythema multiforme	-	1
HIV skin lesions	2	-
Psoriasis	1	1
Seborrheic keratosis	-	1
Squamous papillomas	1	-
Other	2	-
Total	**8**	**10**

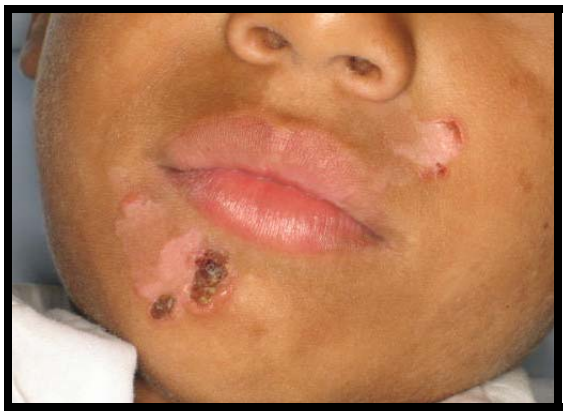


Figure 2

Atrophy and hypopigmentation following healing of peri-oral blisters in boy with Epidermolysis bullosa Simplex

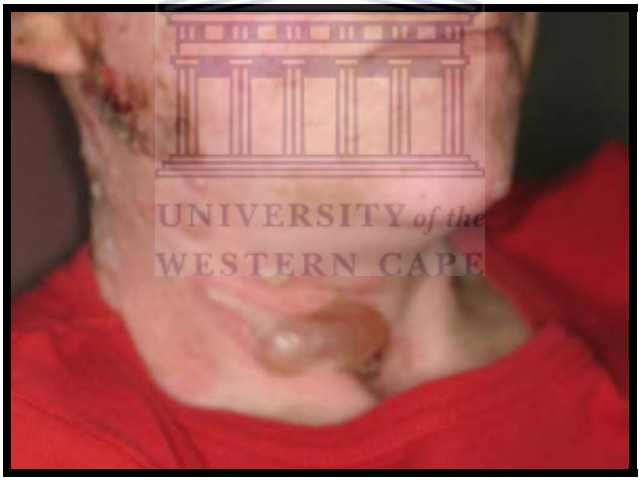


Figure 3

Skin blisters in person with Dystrophic Epidermolysis bullosa

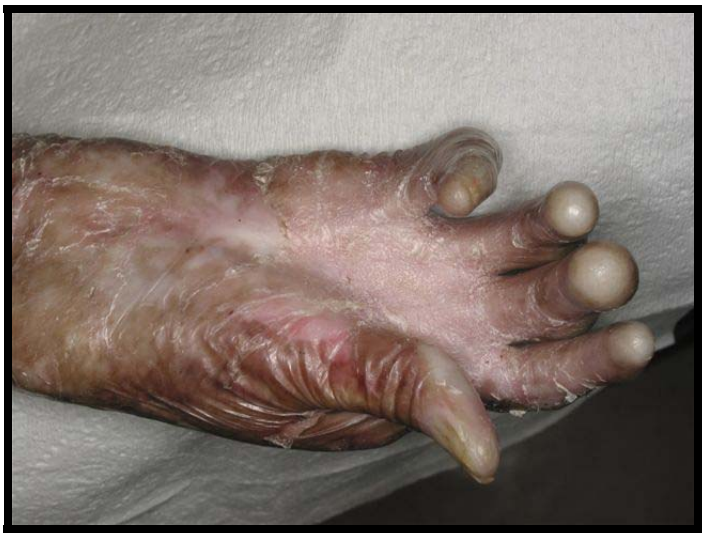


Figure 4

Flexion contractures of right hand with severe atrophic scarring of skin in person with Dystrophic Epidermolysis bullosa

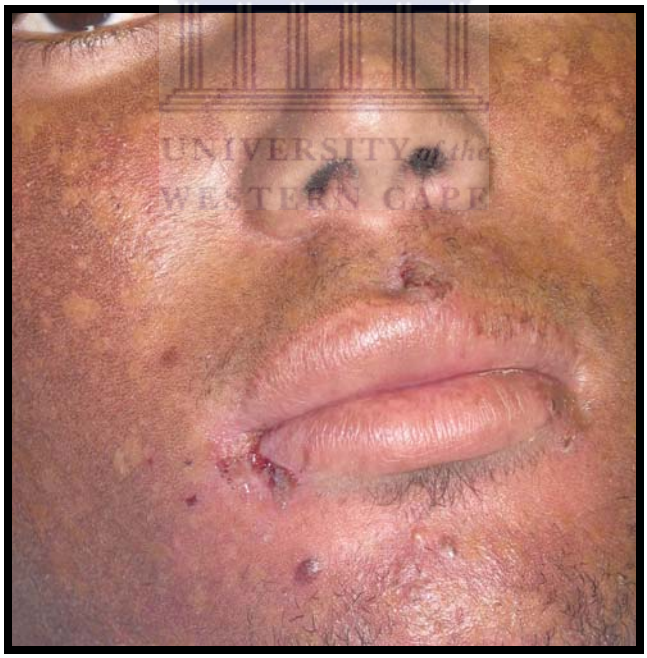


Figure 5

Poikiloderma of the skin and healing peri-oral blisters seen in Kindler syndrome

5. General and dental health questions (Global oral health ratings score)

There were no statistically significant differences with regard to general and dental health questions between the Epidermolysis bullosa and control persons. In fact, all participants with Epidermolysis bullosa (14) rated their general health as "good, very good and excellent" whereas two persons in the control group perceived their general health as "poor or fair".

The distribution for the Epidermolysis bullosa and control persons was similar with regard to the perception of their dental health. "Good, very good and excellent" dental health perception was slightly higher (53.1%) than those persons who perceived their dental health as "poor and fair" (46.9%).

A greater need for dental treatment was expressed overall by participants in both groups (62.5%) compared to those who felt they had "no – very little need" (37.5%).

Twenty-two participants (68.8%) reported that they received advice on how to care for their mouth, with an equal distribution between the Epidermolysis bullosa (10) and control groups (12). The advice on how to care for their mouth was received mostly from dental health personnel.

6. Oral lesions in persons with Epidermolysis bullosa

No significant oral lesions (other than tooth decay) were seen in persons in the Epidermolysis bullosa Simplex group. Oral lesions were present in persons with Junctional Epidermolysis bullosa, Dystrophic Epidermolysis bullosa and Kindler syndrome (Table 9).

A 4mm wide zone of bright gingival erythema was seen in the maxillary anterior region, extending from the marginal to the attached gingival, in only one person with Junctional Epidermolysis bullosa (Figure 6). The lesion did not appear to be plaque related despite her high plaque and gingival indices. Oral ulceration of the soft palate was seen in one JEB patient (Figure 7). The other ulcer was seen on the attached gingival above the first

right premolar. Both ulcers were small (<5mm), well circumscribed, with a white base and surrounded by an erythematous halo. Even though no oral ulcers were seen in the other Junctional Epidermolysis bullosa participant, its incidence was reported to be quite common especially in relation to eating "harder" foods such as toast. Depapillation of the dorsal surface of the tongue (Figure 8) was seen in the same participant as well as thick, ropey saliva. Both JEB individuals had enamel defects with wear of the occlussal tooth surfaces (Figure 9).

Of the two individuals with recessive dystrophic Epidermolysis bullosa, both were female, in the same age range and had a maximal oral opening was 15mm and 24mm respectively (Figure 10). The patient with the most severe microstomia also had ankyloglossia, depapillation of the dorsal tongue, absence of palatal rugae (Figure 11) and predominantly roots remnants in her mouth (Figure 12), with poor oral hygiene. The second recessive dystrophic Epidermolysis bullosa female person exhibited severely worn down teeth covered by excessive amounts of plaque, and gingivae that bled easily. (Figure 13, 14).

Defects in the tooth enamel was recorded in both participants with junctional Epidermolysis bullosa and one person with dystrophic Epidermolysis bullosa, as well as excessive occlussal tooth wear (attrition).

The patient with Kindler syndrome (Figures 15,16), presented with erythematous and inflamed gingiva, with cratering in the maxillary anterior interdental area. The gingiva appeared desquamative, was fragile and bled with even the slightest provocation. Healing peri-oral blisters and angular cheilitis was also seen. His mouth opening was restricted with a maximal oral aperture of 13mm and his tongue extrusion was limited to only the tip of the tongue passing over the lower anterior incisor teeth.

Table 9: Recorded oral manifestations in persons with Epidermolysis bullosa

	JEB	DEB	KINDLER SYNDROME
Oral ulcers/blisters	1	1	____
Atrophy/depapillation of dorsal tongue surface	1	1	____
Atrophy of palatal mucosa	____	2	____
Maximal mouth opening	____	13mm	15mm
Ankyloglossia		1	____
Enamel defects	1	1	____
Occlusal tooth wear	2	2	____
Gingival erythema	maxillary gingival involvement extending from 14-24 (4mm wide)	____	____
Spontaneous gingival bleeding	1	1	1
Angular cheilitis	____	____	1
Desquamative Gingivitis	____	____	1

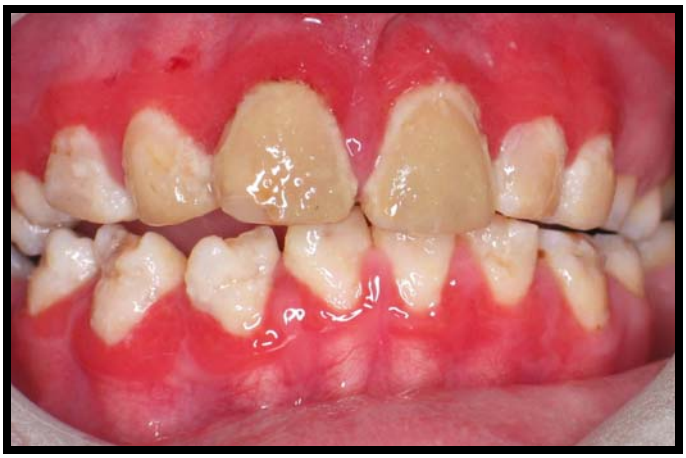


Figure 6

Moderate plaque accumulation and erythema of the marginal and attached gingiva seen in person with Junctional Epidermolysis bullosa

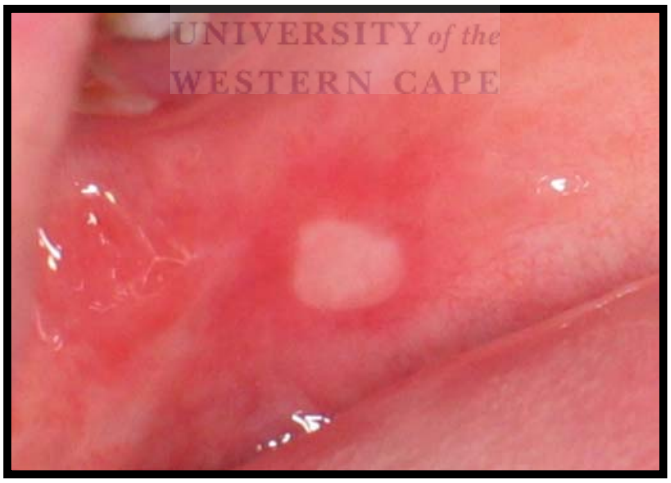


Figure 7

Ulcer on soft palate in person with Junctional Epidermolysis bullosa

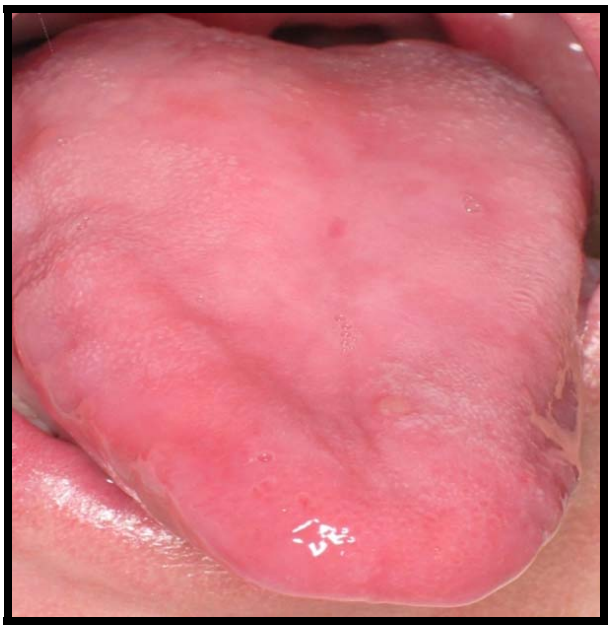


Figure 8

Depapillation on dorsal tongue surface with healing ulcer

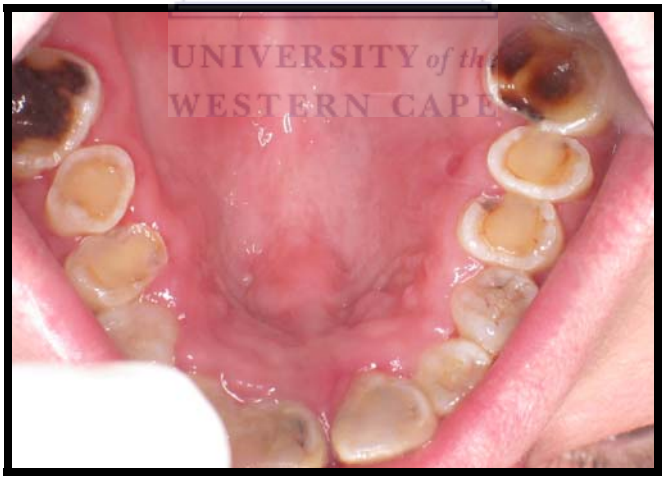


Figure 9

Abrasion of maxillary and mandibular posterior teeth

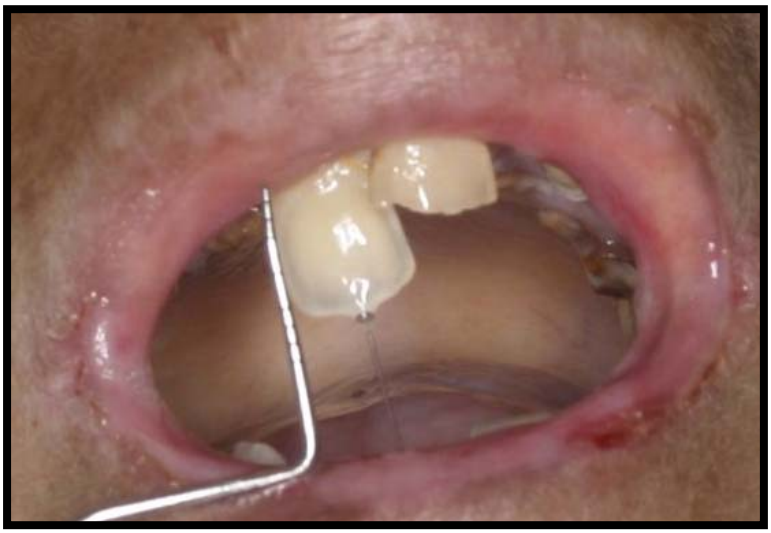


Figure 10

Limited mouth opening of 15mm

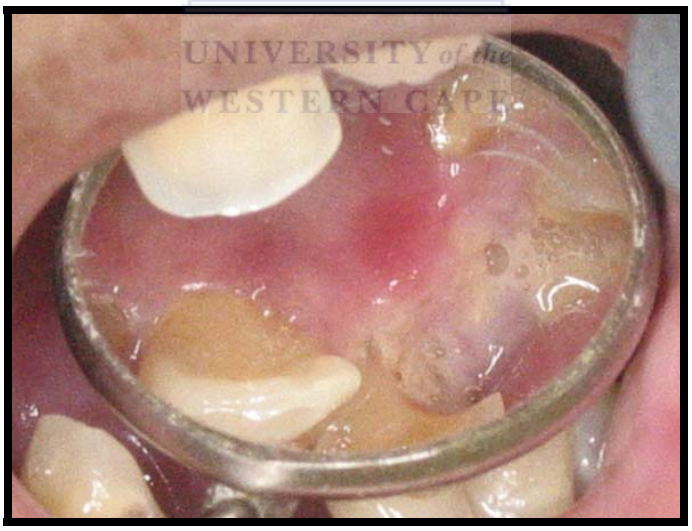


Figure 11

Obliteration of palatal rugae

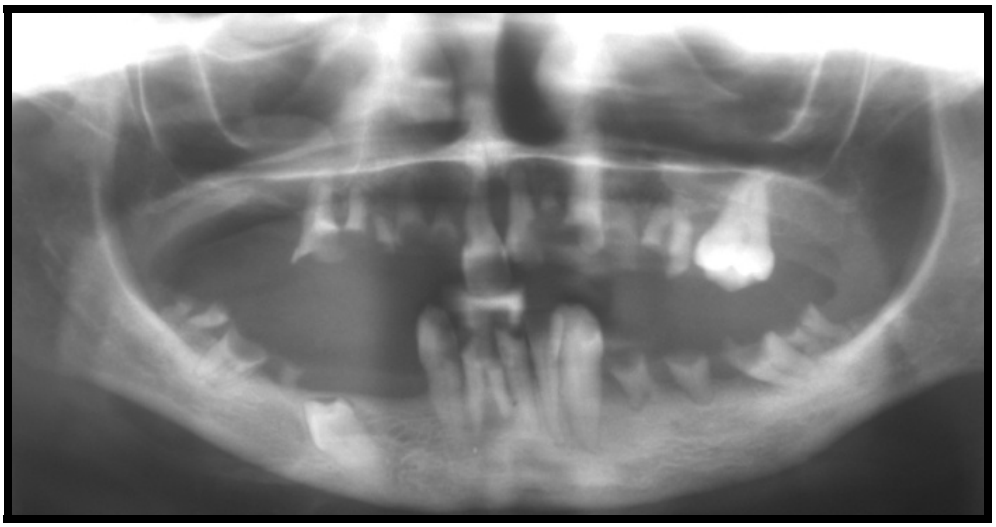


Figure 12

Orthopantomogram showing predominantly root remnants

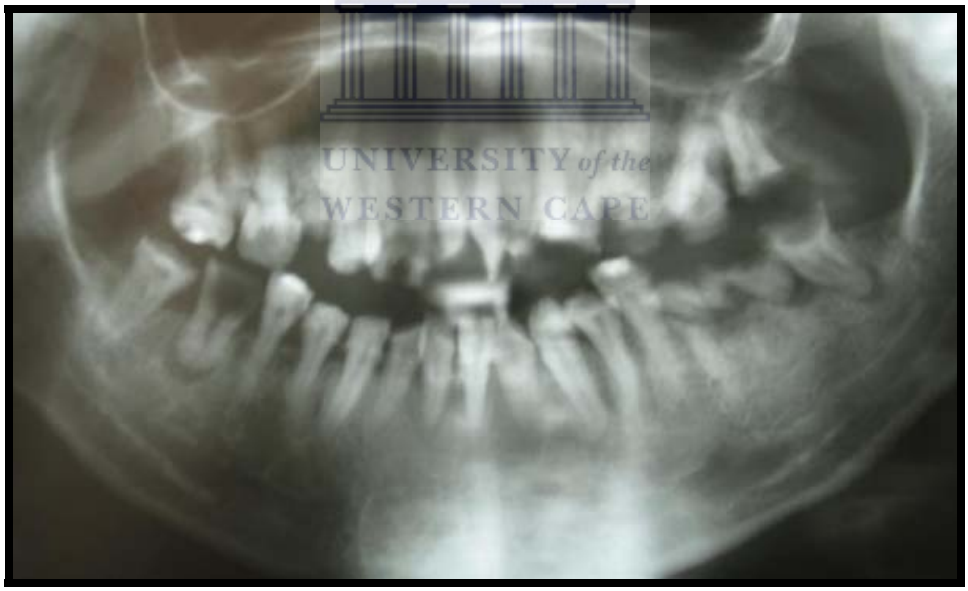


Figure 13

Orthopantomogram of person with Dystrophic Epidermolysis bullosa

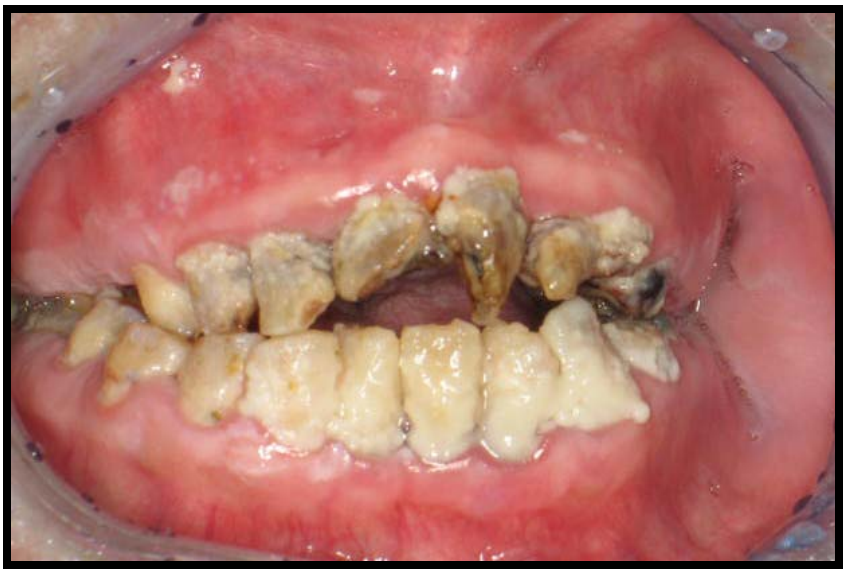


Figure 14

Extensive plaque accumulation and moderately inflamed gingival

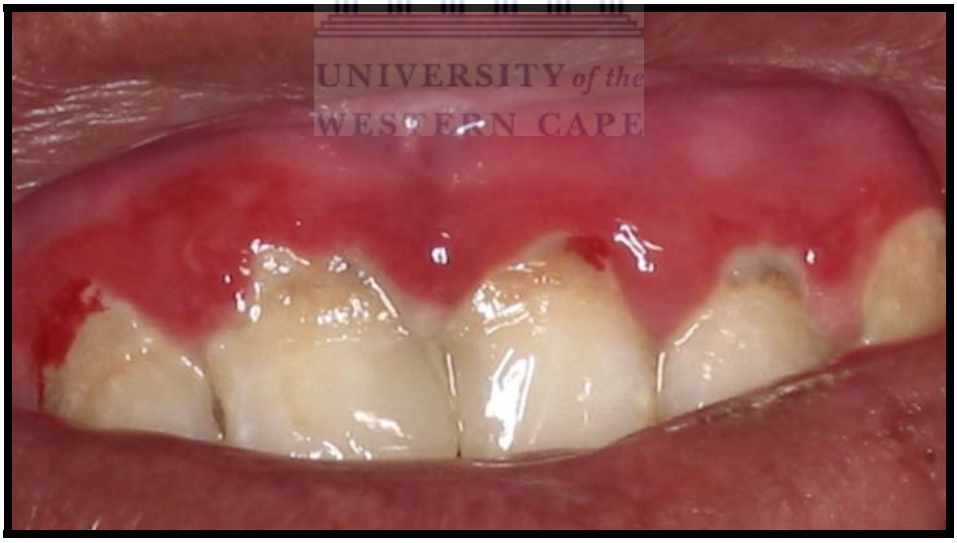


Figure 15

Kindler syndrome – Delicate and reddened (desquamative) attached gingival, probably because of the inherent fragility and increased susceptibility to plaque induced inflammation. There is also blunting of the interdental papillae

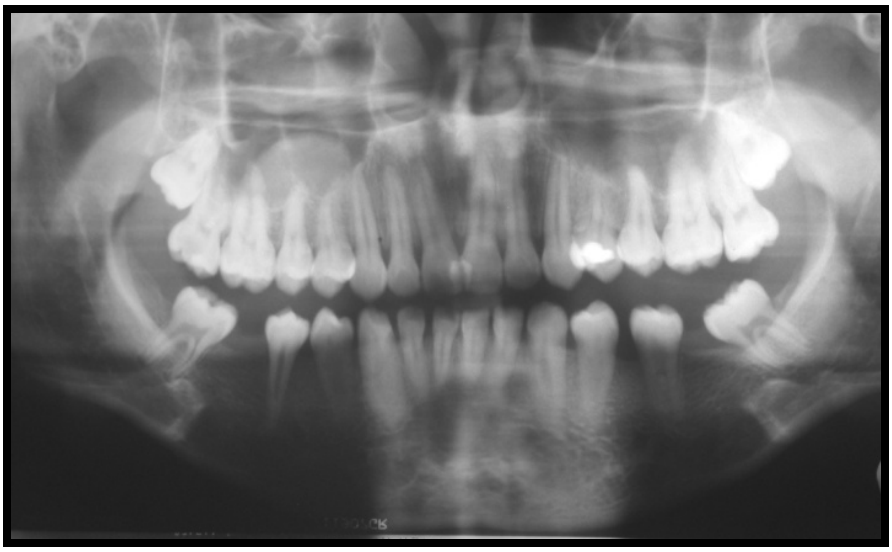


Figure 16

Kindler syndrome – Orthopantomogram

7. **Dental caries experience**

The dental caries status of the Epidermolysis bullosa and control groups varied according to age (Table 10 and 11).

Table 10: dmf values for persons in Epidermolysis bullosa and control groups

	Epidermolysis Bullosa n=5	**Control n=9**
Median	3	2
# Persons with all healthy teeth	1	3
Standard Deviation	2.39	5.88
Minimum	0	0
Maximum	6	18

Table 11: DMF values for persons in Epidermolysis bullosa and control groups

Data	**Epidermolysis Bullosa n=10**	**Control n=14**
Count of TOTAL DMF	10	14
Average of TOTAL DMF	15.30	10.14
# Persons with all healthy teeth	1	5
Standard deviation	10.17	10.88
Min of TOTAL DMF	0	0
Max of TOTAL DMF	28	29

Although not statistically significant (p>0,1) (due to small sample size), the dmf for persons with Epidermolysis bullosa was lower than in the control group as illustrated by the violin plot **(**Figure 17). All of them had Epidermolysis bullosa Simplex (the mildest form). Both dmf distributions for Epidermolysis bullosa and control patients have extremely long tails, but the tail of the control group is extreme, with a maximum of 18. In the control group 3/9 persons had a dmf of zero compared with 1/5 persons with Epidermolysis bullosa.

No statistically significant DMF difference was found **(**Figure 18**)** between the two groups, but the DMF in EB persons (15.3) was generally higher than in the control group (10.1), with no significant difference in the total number of teeth present in the adult Epidermolysis bullosa persons compared to controls.

No adult persons had a DMF score of 0. In the older children's group a DMF score of zero was calculated in 5/14 control persons compared with 1/10 Epidermolysis bullosa persons.

Figure 17: Violin plot of dmf in all Epidermolysis bullosa and control participants

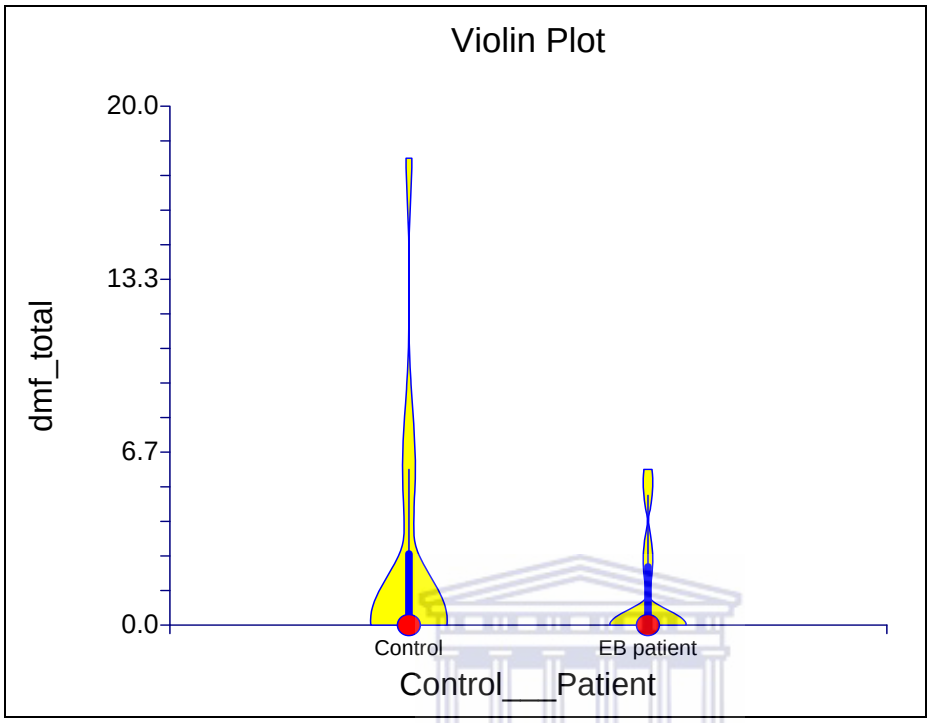
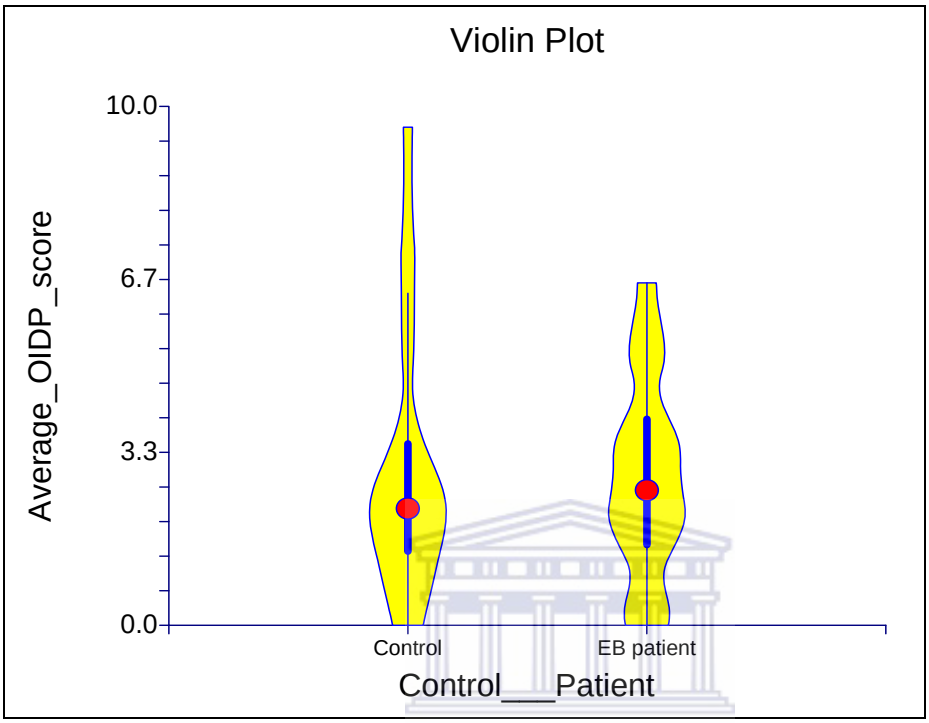


Figure 18: Violin plot of DMF in all Epidermolysis bullosa and control participants



8. Plaque and Gingival index

There was no statistically significant difference with regard to Plaque index or Gingival index between the two groups.

9. Oral impacts on daily performance

Frequency of oral conditions

The frequency of perceived oral conditions reported by the participants in the past 6 months is listed below (Table 12).

As illustrated by Table 12, toothache and tooth decay were the most common complaints in both the Epidermolysis bullosa and control participants. The only conditions which showed statistical significance between persons with Epidermolysis bullosa and the control group were tooth colour, bleeding gums and oral ulceration ($p<0.05$).

Ankyloglossia was seen in 1 person with Epidermolysis bullosa. Limited mouth opening (microstomia) was seen in 3 Epidermolysis bullosa persons and oral ulceration was reported in 7 Epidermolysis bullosa persons. Due to the small sample, no statistical significance was determined.

Table 12: Frequency of perceived oral conditions reported by Epidermolysis bullosa and control participants

	EB persons (n=14)	Control (n=18)
16.1 Toothache	10	14
16.2 Sensitive tooth	4	4
16.3 Tooth decay/Hole in tooth	11	13
16.4 Fractured tooth	4	2
16.5 Tooth loss	2	2
16.6 Loose tooth	1	0
16.7 Colour of teeth	4	0
16.8 Position of teeth	3	2
16.9 Shape or size of teeth	0	1
16.10 Bleeding gums	6	2
16.11 Swollen gums	1	2
16.12 Other gum diseases	3	1
16.13 Calculus	3	2
16.14 Oral ulcer	7	0
16.15 Bad breath	2	4
16.16 Deformity of mouth	1	0
16.17 Noise in jaw joint	0	0
16.18 Improper filling or crown	0	0
16.19 Loose denture	2	3
16.20 Orthodontic appliance	0	0
16.21 Ankyloglossia/Cannot move tongue	1	0
16.22 Microstomia/Difficulty in opening mouth	3	0
16.96 Other	—	—

10. **Oral Impact on Daily Performance (OIDP)**

The reported impacts were centered on daily activities such as eating, speaking and sleeping. No calculations were performed to obtain statistical significance between the two groups because the sample size did not allow the power to detect any significant differences.

Figure 19 and 20 shows the percentage distribution of the OIDP scores in the control (88.9%) and Epidermolysis bullosa group (85.7%) respectively. The overall OIDP score for both groups was high (87.5%).

Figure 19: Stem and Leaf diagram of the OIDP scores in control patients

Stem	***Leaves***
0-4	002
5-9	566788
10-14	01122
15-19	
20-24	0
25-29	6
30-34	0
35-39	8

Figure 19 displays the distribution of the OIDP scores in the control group. This is a long tailed distribution with a tail to the larger values. The median is equal to 9 (the average is equal 11.8). The minimum is equal to zero and the maximum is equal to 38.4. The maximum OIDP score of 38.4 influences the dispersion as calculated by the standard deviation very much.

Figure 20: Stem and Leaf diagram of the OIDP scores in EB patients

Stem	***Leaves***
0-4	003
5-9	788
10-14	01444
15-19	
20-24	02
25-29	6
30-34	
35-39	

Figure 20 displays the distribution of the OIDP scores in the EB group. This is a long tailed distribution with a tail to the larger values. The median is equal to 10.4 (the average is equal 11.3). Comparatively, the tail is shorter compared to that of the control group.

The prevalence of oral impacts on daily performances in the Epidermolysis Bullosa and control groups were calculated by the percentage of participants with OIDP scores more than zero.

Table 13: Prevalence of Oral Impacts on Daily Performances in the two groups: number of respondents with impacts

	OIDP items	Epidermolysis bullosa	Control group	Total
1	Eating	12 (85,7%)	16 (88.9%)	28 (87.5%)
2	Speaking	7 (50.0%)	4 (22.2%)	11(34.4%)
3	Cleaning teeth	3 (21.4%)	9 (50.0%)	12 (37.5%)
4	Light activities	0	2 (11.1%)	2 (6.25%)
5	Vigorous activities	0	2 (11.1%)	2 (6.25%)
6	Sleeping	8 (57.1%)	8 (44.4%)	16 (50.0%)
7	Relaxing	2 (14.3%)	4 (22.2%)	6 (18.75%)
8	Smiling, laughing	5 (35.7%)	10(55.6%)	15 (46.9%)
9	Emotional state	5 (35.7%)	5 (27.8%)	10 ((31,3%)
10	Enjoying contact of other people	5 (35.7%)	4 (22.2%)	9 (28.1%)

CHAPTER 6: DISCUSSION

Hereditary Epidermolysis bullosa is a rare group of mechanobullous disorders. The rarity of the condition made a larger scale study in this population difficult. All studies documenting oral findings in persons with Epidermolysis bullosa are descriptive and report on an international patient pool (**Silva *et al,* 2004; Pekinar *et al,* 2005; Azrak *et al,* 2006; Almaani *et al,* 2008**). Two South African studies of Epidermolysis bullosa (**Menter and Patz**, **1975** and **Winship**, **1986)**, conducted a nationwide survey to delineate the South African Epidermolysis bullosa types and subtypes. To date no South African study has described their oral findings, nor reported on how these findings impact on their everyday life.

The present study included 14 persons diagnosed with hereditary Epidermolysis bullosa, with Epidermolysis bullosa Simplex being the most common. This is contrary to the findings of Winship (1986) who reported dystrophic Epidermolysis bullosa to be the most common variant. This discrepancy could be explained by the geographical restriction of the sample compared to the nationwide South African pool of persons seen in the study conducted by Winship (1986).

Oral manifestations

Oral findings in persons with Epidermolysis bullosa are widely reported in the international literature. Lesion prevalence is expressed according to the Epidermolysis bullosa type and subtype, with the Junctional and Dystrophic Epidermolysis bullosa types dominating the reports (**Almaani *et al,* 2008**). Even though the sample size of our Epidermolysis bullosa participants was small (n=14), the oral manifestations seen in the present study were consistent with other international case reports (**Silva *et al,* 2004; Pekinar *et al,* 2005; Azrak *et al,* 2006**).

The results of this study reveal no distinctive oral manifestations in the Epidermolysis bullosa Simplex type. The absence of oral mucosal lesions in the Epidermolysis bullosa Simplex type may be cumulatively due to the more superficial nature of the lesion

relative to the other subtypes, as well as the inherently high oral mucosal epithelial cellular turnover. This would ensure rapid healing of intra-oral lesions.

In contrast, oral manifestations were more common in persons with recessive Dystrophic and Junctional forms of Epidermolysis bullosa, consistent with those described in the literature. These included oral ulcerations, atrophy of the tongue and marginal gingival erythema. Although earlier case reports have proposed an increased propensity for periodontitis in persons with Kindler syndrome (**Ricketts 1997**), no radiographic evidence of bone loss, or periodontal pocket formation was seen in our patient.

Case reports have described "bad teeth, poor, pitted or discoloured enamel" under the umbrella term "tooth problems". Consensus exists that persons with recessive Dystrophic and Junctional forms of Epidermolysis bullosa have dysplastic teeth more often than in the dominant and Simplex forms of the condition (**Gorlin *et al,* 2007**). Both persons with Junctional Epidermolysis bullosa and one Dystrophic Epidermolysis bullosa participant had dysplastic teeth, pitted enamel and attrition of the occlussal enamel surfaces. The other remaining Dystrophic Epidermolysis bullosa participant displayed mostly root remnants. A reduced enamel mineral content was reported in severe forms of dystrophic Epidermolysis bullosa, but developmental enamel defects were only reported in 8.6% (**Wright, 1993)**. Caries is quite prevalent in these persons because of the reduced or poor oral hygiene and soft food consumption (**Azrak *et al,* 2006**). Our findings are consistent with these and reflected by the high dental caries index.

Limited mouth opening was evident in the Dystrophic Epidermolysis bullosa and Kindler syndrome patients. Ankyloglossia (in the Dystrophic EB patient) and restricted tongue movement in the Kindler patient (limited to tip of the tongue just passing over the lower incisor teeth) was consistent with reports in the literature (**Chimenos *et al,* 2003; Wiebe *et al,* 2008**). It is generally accepted that mucosal involvement increases over time in persons with the more severe types (recessive Dystrophic and Junctional forms of Epidermolysis bullosa). Even though our study had no infants or children in these categories, reports reveal unremarkable oral mucosa on initial examination of these

infants and young children, with no limitations in tongue movement or oral opening. With the inevitable dietary transition, an increased exposure to abrasive food textures and non-nutritive sucking, results in increased bullae formation. The constant blistering and healing results in loss of vestibular sulci, tongue papillae, limitations in tongue movement and oral opening. As a result, the dietary intake of liquid and soft foods is increased and oral hygiene is made difficult due to the fear of blister formation and the anatomical limitations. To this end, poor oral hygiene, caries and moderate plaque accumulations are consistently reported. In our study, the children under five years had low dmf scores (in both the control and Epidermolysis bullosa groups), which seemingly increased with age, a finding that is also common in the general population. In addition to this, the adult DMF average and plaque index scores were higher in the Epidermolysis bullosa group, despite the high number of persons getting advice from dental health personnel. The high plaque scores could perhaps be explained inadequate oral hygiene and the soft diets preferred by persons with junctional Epidermolysis bullosa, recessive dystrophic Epidermolysis bullosa and Kindler syndrome. Even though they have received advice on how to care for their mouths, their dental visits may be restricted to fillings and extractions of carious teeth only.

Response to Global general and Dental health questions

The perceived need (62.5%) for dental treatment was higher than the percentage respondents who expressed “poor to fair” dental health (46.9%). In addition to this, the adult DMF average and plaque index scores were higher in the Epidermolysis bullosa group despite (15.3) despite the high number of persons getting advice from dental health personnel. The high plaque scores could perhaps be explained by soft diets preferred by persons with junctional Epidermolysis bullosa, recessive dystrophic Epidermolysis bullosa and Kindler syndrome. Whilst they have received advice on how to care for their mouths, their dental visits may be restricted to fillings and extractions of carious teeth only.

Moderate to severe blistering of the skin was seen in the Epidermolysis bullosa group. Despite this, all participants in this group perceived their general health as “good, very

good and excellent". Health status and health-related quality of life measures are distinct variables and that poor health does not necessarily translate to a poor quality of life. In fact, many participants in studies of chronic conditions report their quality of life of is good, despite quite severe and clinically obvious physical limitations (**Allen, 2003**). People's perceptions of oral health vary. Thus, the presence of obvious clinical symptoms should not be viewed as a limitation, but as strength, because it allows participants to assimilate their various experiences and decide which ones are the most important.

Interviews

However, data collected via individual face-to-face interviews is time consuming and the possibility of respondents being influenced exists, this method ensures personal contact and is anticipated to facilitate higher response rates (**Katzenellenbogen *et al*, 1997**). In addition, the design of the questionnaire was patient centred. This was ensured via a literature search of reported oral manifestations as well as pre-survey discussions with Epidermolysis bullosa persons with regard to their concerns regarding their oral health. The OIDP questionnaire's format lends itself to ask questions about both beneficial and adverse effects on well-being **(Slade, 1998)**. The other advantage is that the answers can be evaluated as responses to both individual questions and be summarized as numeric scores.

Oral Impacts on Daily Performance (OIDP) Tool

The OIDP has been validated and reliably used in international population based studies in both children and adults. The first South African "exposure" to this tool was validated in a pilot project exploring the use of OIDP measure in specific populations with various cultural settings. In addition, both children and adults were evaluated together. A questionnaire similar to the one validated in the cross-cultural project mentioned above, was used in the present study, which also included children and adults, with an even broader range.

In general, the prevalence of oral impacts on the daily performance did not vary significantly between the two groups, the only exception being light and vigorous

activities. No persons in the Epidermolysis bullosa group attributed any impact of oral lesions on these activities. These activities are either avoided due to the nature of their condition (blistering following minor trauma); or their "life experience" have made them tolerant to any impact thereof.

The present study was designed to encompass objective, quantitative and qualitative research measures. Qualitative analysis using an oral health related quality of life (OHRQoL) measure such as the oral impact on daily performance (OIDP) tool enabled an understanding of the socio-dental impact of perceived oral conditions in everyday life.

Despite the limitations posed by the sample size, the OIDP measure lends insight into the consequences of untreated oral soft and hard tissue lesions. It has also linked the most common oral problems causing impacts and the priorities of dental health care services. Thus, a study was planned with the objective of assessing the prevalence, intensity and extent of impacts attributed to mucosal and hard tissue lesions in persons with Epidermolysis bullosa, by subtype.

While no precise inferences can be made, trends from this study highlights the need for a broader multicentre study using much larger sample sizes and representative persons from each EB subtype. The OIDP tool has validated its use as a socio-dental approach to needs assessment and planning instrument in dental services. The value of employing such a tool has highlighted the need to give more attention to the oral hygiene regimen for these persons. It has also provided some insight into consequences of untreated tooth decay, as well as the benefit of dental treatment thereof.

This enables us to focus our attention on addressing those conditions with the most influence on persons with such chronic conditions.

CHAPTER 7: CONCLUSION

The results of the study show that oral lesions (particularly tooth decay and toothache) in persons with Epidermolysis bullosa do affect their daily activities and the impact thereof is high. Other oral manifestations, irrespective of the subtype, had little impact on the OIDP score. This may be because the EB persons have become tolerant of and "learn to cope" with them.

Recommendations

Epidermolysis bullosa is a rare condition and not all persons with EB will present with lesions. However, all health personnel (including the dental profession) must be cognizant of this condition, in order to manage these persons safely, without incurring harm inadvertently. Thus, the overall management of persons with Epidermolysis bullosa must encompass ways to minimize and prevent trauma; provide an optimum wound healing environment; provide pain management and judicious checks for the development of premalignant lesions. This necessitates a multidisciplinary and holistic approach, with emphasis on patient involvement. To this end, an oral health care programme should form an integral part of their management because of the risk of dental disease. Periodic recall visits will enable the monitoring of home care and minimize the need for advanced restorative procedures. In this way, one may reduce the impact any oral problems may have, so that they do not further influence the patients well being.

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APPENDIX 1: APPROVAL BY ETHICS COMMITTEE

APPENDIX 2: QUESTIONNAIRE

APPENDIX 3: CONSENT FORM

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Table 5: Summary of oral findings seen in recessive dystrophic Epidermolysis bullosa and JEB from case reports

Study	Summary of extra-oral manifestations	Intra-oral lesions
Pekinar *et al*, 2005 **Case 1** Dystrophic recessive EB	-12 year old boy with blistering of the hands, ears, knees, elbows, feet, trunk, scalp, face, anus. Digital webbing with mitten like deformities of the hands were seen and he experienced eating difficulties related to sever blistering intra-oral	- White lesions on tongue, gingiva and buccal mucosa. - Obliteration of palatal rugae and lingual papillae - Microstomia - Rampant caries with poor oral hygiene
Case 2	- Blisters on the hands, feet, ears, nails, face	-Blisters on palate, lips and tongue
Silva *et al*, 2004 **Case 1** Dystrophic recessive EB	- 8 year old boy with feeding difficulties and limited water intake - Digital webbing of hands(mitten-like deformity), - nail dystrophy - Knees, ears affected	- generalized white spot lesions, caries and extensive plaque deposits - delayed occlussal development - blister formation on back of tongue due to trauma from remaining roots - ankyloglossia and microstomia
Case 2 Dystrophic recessive EB	-10 year old male with anaemia and feeding difficulties	- white spot lesions, caries, normal tooth eruption -had 13 teeth extracted by age 8 years
Case 3 Dystrophic recessive EB	-8 year old female with deformed hands and feet as well as anemia	-microstomia and ankyloglossia - Extensive caries with abundant plaque deposits - Trauma associated vesicles and ulcers

Serrano-Martinez *et al*, 2003 **(**35 Dystrophic recessive EB persons0	- Age range of 4-36 years with no reported extra-oral manifestations	-White fibrotic lesions and blisters on tongue -vestibular obliteration, lingual and palatal atrophy and milium cysts - ankyloglossia and microstomia (All persons)
Azrak *et al*, 2006 Dystrophic recessive EB	-7 year old boy, with normal mental development, but -retarded physical growth -generalized blistering present at birth and has mitten- deformity of hands -had severe anemia at age 5 because of bleeding from eroded skin and uses iron tablets sporadically - Diet consists of pureed foods and boiled vegetables due to development of oesophageal stricture -Hyperopia due to corneal opacity (lacrimal glands unaffected)	-loss of tongue papillae Ankyloglossia and microstomia (30mm) Vestibular fundus obliteration -poor oral hygiene despite use of power toothbrush -Orthopantomogram showed normal development of teeth
Almaani *et al*, 2008 Dominant JEB mutation)	- 7 year old girl with trauma-induced skin blisters, erosions and scars on knees - Blisters not present at birth, but arose as a toddler after trauma. Blisters waning over past 2 years	-Abnormal teeth with hypoplastic enamel
Pacheco and de Sousa Araugio, 2008 Dystrophic recessive EB	37 year old female finger and nail involvement -alopecia -constricted larynx	-trismus -poor oral hygiene

Table 7: Summary of salient clinical features in major EBS subtypes

	Autosomal dominant mode of inheritance			Autosomal recessive mode of inheritance		
	EBS localized	**EBS, Dowling-Meara**	**EBS-other generalized**	**Autosomal recessive EBS**	**EBS-Ogna**	**EBS-migratory circinate**
Onset	Early childhood	Birth	Birth	Birth	Birth	Birth
Distribution of skin lesions	Palms and soles (hands and feet)	Generalized	Generalized (scarring)	Generalized, anogenital	Widespread, mostly acral	Generalized
Usual skin lesions	Blisters	Blisters (Herpetiform pattern)	Blisters	Blisters	blisters	Blisters
Milia		yes		rare		
Atrophic scarring				Yes		
Dystrophic/ absent nails	yes	yes	yes	yes		
Keratoderma		Diffuse keratoderma	Focal keratoderma			
Oral manifestations	Intra-oral blisters (25%)	Intra-oral blistering common	Soft tissue lesions rare			
Eye involvement	Absent	Absent	Rare			

Other	No tooth involvement		Exacerbated in warm weather		Bruising tendency	Post-inflammatory brown hyperpigmentation

Table 8: Summary of clinical findings in major JEB subtypes

ONSET						
Distribution of skin lesions						
Usual skin lesions						
Milia						
Atrophic scarring						
Dystrophic/ absent nails						
Keratoderma						
Oral manifestations						
Eye involvement						

Other						

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Table 1: Inherited Epidermolysis Bullosa Types and Subtypes

EB Type	Inheritance Pattern	EB subtype	Target protein (gene)	Ultrastructural site of epidermal tissue separation
EBS	Autosomal dominant	Suprabasal	PKP1 (plakophilin-1) DSP (desmoplakin)	Intra-epidermal, within basal keratinocytes
	Autosomal recessive – (X linked)	Basal	KRT5 (Keratin-5) and KRT14 (Keratin 14) PLEC1 (plectin) ITGA6, ITGB4 (α6β4 integrin)	
JEB		Herlitz	LAMA3, LAMB3, LAMC2 (laminin-332)	Within the lamina lucida of basement membrane
		Non-Herlitz (Other)	LAMA3, LAMB3, LAMC2, COL17A1 (TYPE XVII collagen);ITGA6, ITGB4 (α6β4 integrin)	
DEB	Autosomal recessive	Dominant	COL7A1 (type VII collagen)	Below lamina densa
		Recessive	COL7A1 (type VII collagen)	

Kindler Syndrome			KIND1 (kindling-1)	Mixed cleavage plane

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9 December 2008

To Whom It May **Concern**

I hereby certify that the Senate Research Committee of the University of the Western Cape has approved the methodology and the ethics of the following research project by: Dr H Holmes (Dentistry)

Research Project:	Impact of oral lesions on the quality of life in persons with epidermolysis bullosa
Registration no.:	08/9/30

fter
Development
University of the
Western Cape

Peter Sy
Research

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 **Groote Schuur Hospital Old Main Building**
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

17 February 2009 REG

REF: 076/2009

Dr HK Holmes
Oral Medicine & Periodontology
Faculty of Dentistry & WHO Oral Health Collaborating Centre
University of the Western cape
Private Bag X08
Mitchells Plain

Dear Dr Holmes

PROJECT TITLE: THE IMPACT OF ORALL ESIONS ON THE QUALITY OF LIFE IN PERSONS WITH EPIDERMOLYSIS BULLOSA

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 20th February 2010.

Please send us an annual progress report if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

Please would you include a signature line on the consent for older children (generally 7 years and older) so that they can give their assent to take part. Also note that we do not require a witness's signature unless a parent/participant is illiterate and the consent form was read to them.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REG. REF in all your correspondence.

lemjedi

UNIVERSITY OF CAPE TOWN

Department of Medicine

Division of Dermatology

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4 February 2009

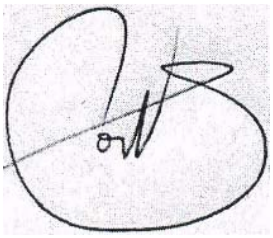
Dear Haly

RE: ACCESS TO PATIENTS WITH EPIDERMOLYSIS BULLOSA ATTENDING DERMATOLOGY AT GROOTE SCHUUR & RED CROSS HOSPITAL

It is permissible for you to access these patients provided you get their permission and have UCT ethics approval of your study.

Pease feel free to contact me should you need any help. Good

luck with this meaningful work. Yours sincerely



Professor Gail Todd FFDerm (SA) PhD
Head: Division of Dermatology

PREVALENCE AND IMPACT OF ORAL LESIONS ON QUALITY OF LIFE IN EB - OIDP Study

Interviewer Administered Oral Health Survey Questionnaire

Introduction:
This interview is about your health, about mouth and teeth problems and about dental treatment. There is no right or wrong answer. Please feel free to ask about anything you don't understand.

1) Study Record Number | | | |

2) Date | D | M | 200 |

3) *Geslag* /Sex | Male | Female |

4) *Hoe oud is jy? (jare)*//Age in years | 12 | 16 | | |

5) Geographic location (CIRCLE ONE) | 1 = Urban | 2 = Rural/small town |

6a) Occupation | |

6b) Type of EB (CIRCLE ONE) | 1 = EBS | 2 = JEB | 3= DEB |

General Health Questions
Now, I am going to ask you some broad questions about your general and dental health:
Nou gaan ek 'n paar vrae oor jou algemene gesondheid vra:

7) In general would you say your health is//*My algemene gesondheid is*:

1	2	3	4	5
Very Poor	Poor	Fair	Good	Very good
Baie sleg	*Sleg*	*Aanvaarbaar*	*Goed*	*Baie goed*

8) In general would you say your dental health is// *My tandheelkundige gesondheid is*

1	2	3	4	5
Very Poor	Poor	Fair	Good	Very good
Baie sleg	*Sleg*	*Aanvaarbaar*	*Goed*	*Baie goed*

9) How satisfied are you with your oral health? *Hoe tevrede is u met jou tandheelkundige gesondheid?*

1	2	3	4	5
Not at all				Very satisfied
Baie ontevrede				*Heeltemaal tevrede*

10) How much do you think you need dental treatment? *Hoeveel benodig jy tandheelkundige behandeling?*

1	2	3	4	5
Not at all				A great deal
Heeltemaal onnodig				*Erg nodig*

11) Have you ever received advice on how to care for the health of your mouth? | **1 =Yes** | **2 = No** |
Het jy ooit advies gekry hoe om jou mond gesond te hou? (Skip to 13)

12) If yes, from where did you get this information? (READ CATEGORIES CODE ALL THAT APPLY)
*As jy **ja** beantwoord het, se asseblief waar jy die informasie gekry het?*

Family/Friends // *Familie of vriende*	1
School // *Skool*	2
TV / radio	3
Dental/Health Personnel // *Tandheelkundige personeel*	4
Newspapers or Magazines // *Koerante of tydskrifte*	5
Other//*Ander bronne* (Specifiy//*Wees specifiek*)	96
Specify…	

OIDP Assessment

Now I would like to ask you if **problems with your mouth, teeth or dentures** have caused you difficulty with any everyday activities in the past 6 months.
Nou wil ek jou vra oor die uitwerking van enige tandheelkundige probleme op jou daaglikse lewe gedurende die laaste ses maande.

(INSERT ANSWERS to QUESTIONS 13-16 IN THE **OIDP ASSESSMENT Chart** ON NEXT PAGE).

13) In the past six months, have you had any of the problems mentioned in the OIDP Chart below.
G*edurende die laaste ses maande, het jy enige van die volgende probleme ontvaar?*

(CIRCLE EITHER "Y" OR "N" IN THE OIDP CHART)
(If answer is **Yes**, GO TO QUESTIONS 14-16 WITH **THIS** DIMENSION)
(If answer is **No** REPEAT QUESTION 13 WITH **NEXT** DIMENSION)

14) During the past six months how often have you had this problem (INSERT DIMENSION)?
G*edurende die laaste ses maande, hoe gereeld het jy **hierdie** probleem ervaar?*

(READ ANSWERS AND CODE IN THE OIDP ASSESSMENT CHART)

Minder as een keer per maand//Less than once a month	1
Een tot twee keer per maand//Once or twice a month	2
Een tot twee keer per week//Once or twice a week	3
Drie tot vier keer per week//Three to four times a week	4
Amper elke dag//Every, or nearly every, day	5

15) Using a scale from 0 to 5, where 0 is no effect and 5 is a very severe effect, which number would you say reflects the effect this problem had on your daily life?
Hoe sou jy hierdie probleem op 'n skaal van nil tot vyf tel, as nil beteken geen uitwerking en vyf beteken 'n enorme uitwerking?

(CODE ACCORDINGLY IN THE OIDP ASSESSMENT CHART)

0 1 2 3 4 5

No effect — *Geen uitwerking*

Very severe effect — *Enorme uitwerking*

16) To which condition(s) do you attribute this impact?
Aan watter rede(s) sou jy hierdie uitwerking toeskryf?

(READ CATEGORIES, CODE ALL THAT APPLY)

Different conditions	**Code**
Tandpyn//Toothache	1
Sensitiewe tande//Sensitive tooth	2
Tandbederf, 'n gat in jou tand//Tooth decay, hole in a tooth	3
Gebreuke tand//Fractured tooth	4
Verlies van 'n tand(e)//Tooth loss	5
Los tand(e)//Loose tooth.	6
Gekleur van tande//Colour of teeth	7
Rangskikking van jou tande//Position of teeth (crooked, gap)	8
Vorm of grootte van tande//Shape or size of teeth	9
Tandvleis wat bloei//Bleeding gums	10
Opgeswelde tandvleis of absess //Swollen gums, gum abscess	11
Ander tandvleis siektes//Receding gums, gum disease, pyorrhoea	12
Tartar of graweel// Calculus,	13
Mondsweer//Oral ulcer or sore spot	14
Stink asem//Bad breath	15
Mondmismaaktheid//Deformity of mouth or face (cleft lip, cleft palate)	16
Snaakse geluide by kakabeen lit//Clicking or grating noise in jaw joint	17
Tandstopsel verkeerde kleur of afgebreek//Improper filling or crown	18
Tandstelsel los//Loose ill fitting denture or plate	19
Ortodontiese stel//Orthodontic appliance, wires or bands	20
Ander rede//Other (SPECIFY//Wees spesifiek)	96

OIDP Assessment Chart

Dimensions	**Questions**			
As jy…../When you are…	13 Y/N	14 Frequency	15 Severity	16 Condition
Kos eet//Eating Food	Y/N			
Suiwer wil praat//Speaking clearly	Y/N			
Tande skoonmaak//Cleaning your teeth/dentures	Y/N			
Huishoudelike werk//Doing light activities such as household cleaning and maintenance, working on a car, playing games	Y/N			
Kragtige aktiwiteit//Vigorous activities such as running, lifting heavy objects, strenuous sports	Y/N			
Slaap//Sleeping	Y/N			
Ontspan//Relaxing - reading, watching TV, listening to music	Y/N			
Glimlag of lag//Smiling, laughing and showing teeth without embarrassment	Y/N			
Dit laat my meer emosieneel voel//With your emotional state, for example, becoming more easily upset than usual	Y/N			
Gemaklikheid by vriende and familie//Enjoying the contact of other people, such as relatives, friends or neighbors	Y/N			

***Gesondheid aktiwiteite*//Health Behaviours**

Now, I would like us to focus on some basic behaviours that are related to health.
Nou wil ons oor sekere gesondheids aktiwiteite praat.

17) Did you clean your teeth yesterday?
Het jy jou tande gister skoongemaak?

1 =Yes	**2 = No**
	(Skip to 20)

18) How many times did you clean your teeth yesterday?
Hooeveel keer het jy jou tande gister skoongemaak?
(READ ANSWERS)

Eenkeer//Once	1
Tweekeer//Twice	2
Meer//More than twice	3

19) Which of the following items did you use to clean your teeth?
Wat het jy gebruik om jou tande skoon te maak
(READ ANSWERS, CODE ALL THAT APPLY)

SPECIFY ……..

Toothbrush/*Borsel*	1
Chewing stick/*stok*	2
Finger/*Vinger*	3
Fluoride toothpaste	4
Floss	5
Toothpick	6
Mouthrinse/*Spoel*	7
Other...SPECIFY	96

UNIVERSITY OF THE WESTERN CAPE

FACULTY OF DENTISTRY

INFORMED CONSENT FOR ORAL EXAMINATION

Dear .....

I am from the Department of Oral Medicine and Periodontology at the University of the Western Cape Dental Faculty. I would like to ask you some questions about yourself, examine your mouth and teeth to look for any problems. This is part a research project to see if you have any oral problems and assess how we can prevent and help you with these problems.

The procedure will take about 10-15 minutes. There are no risks in participating, with no more discomfort than in a routine dental check up examination. All information gathered in the study will be treated as strictly confidential. No one will have access to this information except the researcher. If you agree, photographs of oral problems will be taken stored in such a way as to keep it as confidential as possible.

You are completely free to take part or not to take part in the study. If you decide that you do not want to be part of the study, this will not be held against you.

If you are willing to take part in the study, please sign the form below to allow us to proceed with the examination. If you would like to withdraw from the study at any point or for any reason, please feel free to do so and no questions will be asked.

If you have any questions or queries or would like more information about the study please contact Dr Haly Holmes on telephone number (021) 937 3167/8 ; fax (021) 931 2287; e-mail hholmes@uwc.ac.za or 0832311633.

Thank you for your cooperation

Yours sincerely

Dr Haly Holmes

I have understood the instructions and information given to me and I agree to participate in the study. I have not been forced to participate in the above-mentioned study.

Name: ....
(in block letters)

(Signature/Parent/Guardian)

Date: .....

UNIVERSITEIT WES-KAAPLAND

FAKULTEIT TANDHEELKUNDE

TOESTEMMINGSVORM VIR MOND ONDERSOEK

Geagte …….

Ons is van die Departement Gemeenskapstandheelkunde, Universiteit Wes-Kaapland. Ons wil u graag ‘n paar vrae vra omtrent uself en u mond en tande ondersoek om vas te stel of daar enige probleme is. Dit is deel van ‘n navorsings project en ons doen hierdie ondersoek om vas te stel hoe ons probleme met u mond en tande kan voorkom, en as daar reeds probleme is, u daarmee te help.

Die ondersoek neem ongeveer 10-15 minute. Daar is geen risikos aan deelname nie en die ongemak wat u sal verduur sal soortgelyk aan ‘n roetine tand- en mondondersoek wees. Alle inligting versamel sal streng vertroulik hanteer word. Niemand behalwe die navorser sal toegang tot die inligting hê nie. U naam of enige inligting wat u mag identifiseer sal in die verslae van hierdie studie gebruik word nie. Alle inligting versamel sal so konfidensieel moontlik geberg word.

Inligting wat u omtrent uself verskaf is ook streng vertroulik. Dit is u eie keuse of u wil deelneem aan hierdie studie. Daar sal geensins teen u gediskrimineer word indien u deelneem of nie deelneem nie.

Indien u bereid is om deel te neem aan hierdie studie, teken asseblief die onderstaande vorm om ons toe te laat om voort te gaan met die ondersoek. Indien u op enige stadium van die ondersoek en studie wil onttrek is u nie gebind nie en geen vrae sal gevra word nie.

Enige vrae en navrae, of indien u meer inligting verlang skakel asseblief met Prof Neil Myburgh by telefoon nommer (021) 937 3150; faks (021) 931 2287; e-pos nmyburgh@uwc.ac.za of na-ure by (021) 6833395.

Dankie vir u samewerking

Professor Neil Myburgh

Ek verstaan die inligting en gee hiermee my toestemming om deel te neem aan die studie. Ek was onder geen verpligting geplaas om deel te neem aan bogenoemde studie nie.

Naam:…… Handtekening:……(Ouer,gesinslid)
(in drukskrif)

Getuie: ……..

Datum: …….