Systemic disorders and their influence on the development of dental hard tissues: A literature review

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1. Introduction

Normal dentition develops from the dental lamina originating from a string of epithelial cells in the oral ectoderm during the first months of embryonic development. In each jaw 10 tooth buds corresponding to the deciduous teeth then develop. By the end of the seventh month in utero the development of all tooth buds is complete and the formation of their hard tissues (enamel and dentine) begins. The development of the permanent incisors and premolars is initiated in the fifth month in utero and lasts to the tenth month after birth with the development of the permanent molars continuing through the first years of life. More importantly, the developing tooth bud has been shown to be sensitive to a wide range of systemic disturbances and, enamel particularly, is generally unable to recover once it is damaged. Consequently enamel defects can...
be caused by numerous factors occurring throughout the
development of the teeth from before birth to adulthood.
These may include host traits, genetic factors, immunological
responses to cariogenic bacteria, saliva composition, environ-
mental and behavioural factors and systemic diseases.2,3

The extensive variety of factors which can affect the
development of hard tissue within the mouth means that
defects in enamel and dentine can present with a wide
spectrum of clinical features. These may be generalised and
seen in many teeth or the whole dentition or localised to one or
two teeth. In addition, the defects may affect one surface of
the enamel or be evident throughout its full thickness, and
may be symmetrical or asymmetrical across the midline of the
dentition. Furthermore, defects such as differences from the
normal appearance, colour and texture of the tooth, altered
translucency and pitting, grooving or missing enamel may
result from very different causes including hypomineralisa-
tion, growth reduction, hypoplasia or dysplasias and drug
treatments.

Systemic disorders which affect the formation and devel-
lopment of dental hard tissue as part of, or secondary to, the
disease process may be very complex and have many varying
effects on different organs within the individual. They can
generally be divided into primary or secondary systemic
disorders. Primary disorders are classified as originating or
affecting several organs right at the outset of the disease and
include genetic, hereditary and developmental diseases.
Secondary disorders may be triggered by a particular event
such as changes in hormone levels, trauma, onset of a disease
and viral infections. These diseases and their spectrum of
clinical manifestations on the organs affected (including the
dentition) necessitate an increased knowledge by dental
practitioners of the disease processes, aetiology, relevant
management strategies and prognosis, and must encompass
more than simply the management of the dental require-
ments of the patient.

This review focuses on the effect of systemic disease on the
incidence and extent of damage in dental hard tissues and on
relevant treatment needs of patients.

### 2. Systemic disorders affecting dental hard
tissue development

#### 2.1. Cystic fibrosis

Cystic fibrosis (CF) is the most common lethal autosomal-
recessive disease in the Caucasian population.4 It is char-
acterised by a severely altered function of the absorbing
and secreting epithelia due to abnormal water and electrolyte
transport and pH regulation, and stems from a mutation of the
cystic fibrosis transmembrane regulator protein (CFTR).5,6
These defects result in a chronic disease of the respiratory
and gastrointestinal systems, elevated sweat electrolytes, im-
paired reproductive function, retarded growth and develop-
ment with delays in dental and skeletal maturation.5,7,8
Clinical symptoms of the disease can range from few or no
diagnostic symptoms to the full range, although the diagnostic
criteria for CF includes a sweat chloride level greater than
60 meq/L and at least two of the following symptoms: chronic
obstructive pulmonary disease, exocrine pancreatic insuffi-
ciency or a familial history of CF.9

Once diagnosed, most CF sufferers respond well to
nutritional therapy of a high calorie, high fat diet including
pancreatic enzymes replacement therapy and vitamin sup-
plementation, and infant formulas comprising of protein
hydrolysates and medium chain triglycerides used during the
first years of life. High sugar foods are often consumed in order
to maintain the increased calorific intake needed. Appropriate
antibiotics, including penicillins, cephalosporins or trimetho-
prim-sulfa formulations, are used to combat the respiratory
infections associated with CF.5,10

The delays in dental and skeletal maturation observed in
CF patients are adequately treated by ensuring an appropriate
nutritional intake and are often resolved if survival to the
second or third decade of life occurs.5 Due to the high sugar
containing food consumed by CF patients in order to maintain
their elevated calorific and salt intake, it might be assumed
that the caries incidence among these patients may be higher.
However, the caries incidence has been reported to be lower in
CF patients than in an age-matched healthy population, with
less dental plaque and gingivitis, though increased enamel
defects (opacities) have been observed in CF children.8,11,12 It
has been suggested that the reduced caries rate may be related
to the effects of long-term antibiotic, pancreatic enzyme
replacement therapy and patient awareness on the extent of
oral microbacteria. In addition, CF is associated with patho-
logical effects on the major salivary glands primarily associ-
ated with duct obstruction, and a saliva composition showing
increased levels of calcium, higher mean pH and increased
buffering capacity.5,13 This higher calcium content and
buffering capacity may provide an additional explanation for
a reduction of dental caries which favours tooth reminer-
alisation and is consistent with the observed increased
prevalence of dental calculus on the teeth.5,12,13

Many CF patients have been reported to present with a
higher frequency of enamel hypoplasia (ranging from 5% to
44%) than the healthy population; this may be attributed to the
disease itself or be a consequence of treatment.11,12,14 Many of
the original oral manifestations associated with CF were related
to the use of antibiotics, in particular tetracycline therapy,
where high incidences of tooth discoloration (24%) and
hypoplasia (25%) have been reported.8,15 This prompted the
use of alternative antibiotics with a resultant reduction in the
enamel defects associated with tetracycline therapy. With
respect to the other enamel defects observed in patients with
CF, it remains unclear which relate to the management of
disease and which relate to the disease process itself. Mineral
analysis of the enamel of the teeth of CF patients have indicated
equivalent levels of zinc and phosphorus but decreased levels of calcium when compared with healthy
individuals.16,17 In addition, CFTR has been shown to regulate
the carbonic acid buffer system which plays a pivotal role in
pH regulation within numerous tissues and cells and has been
proposed as the main buffering system in developing
enamel.5,18 The regulation of pH has been shown to be
essential for apatite deposition, crystallite growth, protein-
ase optimisation and function of ameloblasts within the
developing enamel. Studies in a transgenic CFTR knockout
mouse (CF mouse), proposed as a model for CF in humans,
demonstrated a clear role for CFTR function in pH regulation during the maturation phase of enamel formation, particularly in the mouse incisor.\textsuperscript{6} It was shown that calcium was present in distinct bands within the normal mouse incisor corresponding to areas of neutral pH which were absent from the CF mouse incisors. In addition, normal mouse enamel matrix pH was generally higher and modulated differently than the CF mouse enamel. It has been postulated that a reduced pH results in a lack of calcium influx during enamel maturation and hypomineralisation in CF.\textsuperscript{6}

Further molecular studies using the transgenic CF mouse have clearly shown that the CFTR gene is expressed in developing teeth and other mineralised tissues and is associated with abnormal development of incisors.\textsuperscript{19–23} Wright et al.\textsuperscript{22,23} showed that all CF mice had soft, chalky white incisor enamel compared to hard, yellow-brown in normal mice. They exhibited premature degeneration of ameloblasts with increased retention of enamel matrix proteins and a decreased mineralisation of the enamel. Further studies, using energy-dispersive X-ray spectroscopy, demonstrated decreased chloride in the secretory stage CF enamel, with increased iron and potassium and decreased calcium in the CF mature enamel indicating a critical role for CFTR in enamel formation.\textsuperscript{19} Gawenis et al.\textsuperscript{20} concluded that CFTR played a pivotal role in continuously growing incisors but could demonstrate no role for CFTR in the mineralisation of molars or bone in CF mice. They further concluded that the multiple changes in the mineral composition of CF incisors suggested an indirect role for CFTF in several functions such as maintaining the normal salivary environment. Interestingly, they showed that the iron content of CF mouse incisor was markedly reduced, in contrast to the results reported by Arquitt et al.\textsuperscript{19} and may explain the differences in pigmentation seen between normal and CF mouse teeth. Differences in the methods employed in taking the measurements may account for some of these discrepancies. Nevertheless, the complexity of the processes and the need for more studies to clarify the role of CFTR in the formation of hard tissues within the mouth are clearly demonstrated.

The complexity of the processes controlling development of the hard tissues in the CF patient emphasises the need for regular and frequent dental care allowing the reduction in the suffering and medical costs associated with treating this disease. In addition, the increased prevalence of enamel defects and calculus accumulation reinforces the need for early involvement of paediatric dentists in the management and long-term care of these patients.

\subsection*{2.2. Human immunodeficiency virus/acquired immune deficiency syndrome}

Oral manifestations of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome (AIDS) are, generally, a feature of disease progression and occur in approximately 30–80\% of the affected population. Factors which have been shown to predispose patients to oral manifestations include low CD4 T cell levels, high viral load, xerostomia, poor oral hygiene and smoking.\textsuperscript{24–26} Oral lesions can be differentiated as fungal, bacterial or viral infections, neoplasms such as Kaposi’s sarcoma and non-specific presentations such as aphthous ulcerations and salivary gland disease.

Studies investigating the prevalence of oral lesions in HIV/AIDS patients have reported cases of angular cheilitis in approximately 29\% of patients, parotid gland bilateral enlargement, erythematous candidiasis and pseudomembranous candidiasis in approximately 18\% of patients, and conventional gingivitis in approximately 13\% of patients. In addition, herpes simplex virus infections, hairy leukoplakia, recurrent aphthous ulcers and condyloma acuminatum have been seen in up to 6\% of patients.\textsuperscript{26,27} Although enamel hypoplasia was seen in 24\% of patients in one study, the authors concluded that this could not be attributed specifically to HIV infection, but other factors such as oral hygiene.\textsuperscript{27} In addition, a study investigating alveolar bone loss in HIV and AIDS patients compared to matched controls concluded that smoking but not HIV status was the primary factor involved in the alveolar bone loss, further emphasising the complexity of assessing the disease and its effects in HIV/AIDS patients.\textsuperscript{28}

Nevertheless, since the advent of highly effective anti-retroviral therapies the overall prevalence of oral manifestations in HIV patients decreased significantly from 47.6\% to 37.5\%, with decreases primarily in hairy leukoplakia and necrotising periodontal disease. No significant decreases were seen in oral candidiasis, aphthous ulcers, herpes simplex virus lesions and Kaposi’s sarcoma. However there was an increase in HIV associated salivary gland disease from 1.8\% to 5.0\% with associated xerostomia and incidence of oral warts.\textsuperscript{25,26}

Xerostomia is a common complaint of HIV patients and can be caused by a number of factors including salivary gland disease, high viral loads, smoking and HIV medications.\textsuperscript{25,29} The change in quantity and quality of saliva may, in turn, lead to increased dental decay and therefore meticulous oral hygiene is critical in reducing and/or preventing oral disease in these patients.

Treatment of oral diseases in HIV/AIDS patients is reportedly very low, adding to the difficulties in accessing information about the management of some of the more common manifestations of the disease and the differentiation of one manifestation from another.\textsuperscript{30,31} Effective dental management, however, is fundamental to the overall care and health of these patients. Significant advances in understanding the pathogenesis and progression of this disease will ultimately lead to improved care of this patient population.

\subsection*{2.3. Leukaemia}

Many dental manifestations of leukaemia have been reported, including delayed dental development, hypoplasia, agenesia, V-shaped root and shortened root, taurodontia, mucosal pallor secondary to anaemia, microdentia, odontalgia, ulceration of the palate, gingival bleeding, gingivitis, petechiae and ecchymoses of the hard and soft palate, tongue and tonsils.\textsuperscript{32–35} In addition, chemotherapy-induced mucositis and infections, including herpes simplex ulcers and oral candidiasis are commonly observed complications of leukaemia in the oral cavity.\textsuperscript{33,34} Gingival hyperplasia secondary to leukaemia cell infiltration and xerostomia caused by chemotherapy are other noteworthy manifestations.\textsuperscript{34} Pallor, spontaneous haemorrhage, petechiae and ulceration have been described to occur
more frequently in acute than chronic leukaemia.35 Gingival hyperplasia is, generally, more common in acute than chronic leukaemia, in adults and in people with “aleukaemia” or “subleukaemic” forms of leukaemia.36 Nonetheless, the development of gingival infiltration is unpredictable, though leukaemia cell gingival infiltrate is not observed in edentulous individuals, suggesting that local irritation and trauma associated with the presence of teeth may play a role in the pathogenesis of this abnormality.36

Conflicting results have been reported on the caries profile of children treated for malignant disease. An increased rate of dental caries has been reported in some studies where more mild opacities were observed in patients receiving combination chemotherapy for malignant disease compared to controls.32,37,38 Other studies have reported no difference in dental caries between treated children and their siblings, though significantly more dental anomalies were detected radiographically in the chemotherapy treated group.39 The long-term effects of bone marrow transplantation for leukaemia showed a negative impact on missing or filled permanent teeth (DMFT) index based on multiple post-bone marrow transplantation factors with age as a crucial factor in determining the developmental defect of enamel and root.40 This study and others highlight the difficulties for dental practitioners in diagnosing and treating the impact of the disease and its treatment on the development of both deciduous and permanent dentition. It is, therefore, important for a dental practitioner to take into consideration the impact of the disease and its treatment, particularly in respect of immunosuppression where dental interventions may become life-threatening. In general, surgery should be avoided. However dental extractions of carious teeth prior to immunosuppressive therapy may be necessary, as the risks of bacterial infection may outweigh the risks associated with surgical procedures.

New cutaneous lesions, oral or otherwise, are often the initial physical finding that leads to a diagnosis of leukaemia and, in particular, in a patient with known myeloproliferative disease, these findings often herald the development of a more aggressive disease with a poorer prognosis. Therefore, it is important for dentists and physicians to recognise mucocutaneous manifestations of systemic malignancies and to provide the necessary care at all stages of the patients’ treatment.41

2.4. Alstrom syndrome

Alstrom syndrome is a rare autosomal recessive inherited disorder characterised by progressive blindness, deafness, early-onset type 2 diabetes mellitus, obesity, and short stature.42 The mutated gene, ALMS1, which must be inherited from both parents, was identified, though little is known about how this gene causes the disorder.43 There is limited information available on this disorder due largely to its rarity and only one report summarising the oral findings from two cases of Alstrom syndrome from the same family.44

In one report the oral findings from two patients aged 14 and 20 years, both with physical and clinical characteristics consistent with Alstrom syndrome, showed the presence of gingivitis with poor oral hygiene. Both had missing or decayed teeth with radiographs revealing vertical and horizontal alveolar bone loss. In addition, light yellow-brown discoloured enamel bands were observed on the anterior teeth which were characteristic of a moderate form of systemic band-like enamel hypoplasia. Interestingly, this appeared to correlate with tooth development which occurred between 2 and 3 years of age since both siblings showed the same growth lines within the same limited area of the crowns of permanent teeth. This suggests that the enamel hypoplasia was associated with an aetiological factor of the syndrome itself which caused the abnormality at the same age and same stage of tooth formation.

Numerous studies have shown that diabetes mellitus can directly affect the mineralisation and development of bone and teeth with reduced mineralisation and defects in teeth observed in children of diabetic mothers, diabetic adults and in animal studies.45–50 Since it has been shown that Alstrom syndrome is associated with early-onset diabetes mellitus, it may be reasonable to postulate that the presence of diabetes mellitus secondary to the syndrome itself may also have an effect on patient dentition.42,51 Although the exact mechanism whereby diabetes affects hard tissue development is as yet unclear, there is a suggestion from studies using animal models that diabetes may disrupt the mineral composition in teeth and the normal process of amelogenesis.46,47

Further reports of oral findings from patients with this syndrome are required in order to consolidate the findings to date and to assist dental practitioners in the management of these patients.

2.5. Hypophosphatasia

Hypophosphatasia is an inherited metabolic bone disease that results from a deficiency of the enzyme alkaline phosphatase (ALP) in the bone and serum.52–54 It is one of several disorders that resembles osteogenesis imperfecta and is characterised by defective bone and teeth mineralisation with premature loss of dentition. It is caused by abnormalities in the ALP gene leading to the production of inactive ALP protein.55–57 Subsequently, several chemicals, including phosphoethanolamine, pyridoxal 5′-phosphate (a form of vitamin B6) and inorganic pyrophosphate, accumulate in the body and are found in large amounts in the blood and urine. It appears that the accumulation of inorganic pyrophosphate is the cause of the characteristic defective calcification of bones seen in infants and children (rickets) and in adults (osteomalacia).52,54,55 The severity of hypophosphatasia is variable, ranging from the most severely affected failing to form a skeleton in the womb resulting in stillbirth to mildly affected patients showing only low levels of ALP in the blood with no bone problems. In general, patients are categorised as having perinatal, infantile, childhood or adult hypophosphatasia depending on the severity of the disease and the age at which the bony manifestations are first detected. In addition, odontohypophosphatasia is a disease in which children and adults have only dental, not skeletal, problems, usually involving premature loss of teeth and/or wide pulp chambers that predisposes them to cavities and dental caries.52,53,58,59 The clinical forms of this disease tend to have different modes of history and presentation. However, both autosomal recessive and autosomal dominant patterns of inheritance have
been demonstrated for the childhood, adult and odontohy- 
possphatasia forms.\textsuperscript{52,53,56,57,60}

One of the main characteristics of all forms of hypophos- 
phatasia is the loss of dentition. In particular, premature loss 
and changes in the deciduous teeth and/or severe dental 
caries have been reported and remain, along with low levels of 
ALP, one of the main diagnostic features of hypophosphata-
sia.\textsuperscript{56,59-61} In general the anterior deciduous teeth are more likely to be affected and the most frequently lost are the 
incisors. In addition, dental X-rays show reduced alveolar 
bone and enlarged pulp chambers and root canals.\textsuperscript{62,63} Histological analysis suggests that lack of cementum may 
be the cause of the premature tooth loss.\textsuperscript{56,59} Comparison of 
teeth from children with hypophosphatasia with normal 
controls showed that both acellular and cellular cementum 
was affected, though no differences were observed in the 
mineral content of dentin.\textsuperscript{59} Further analysis for the expres-
sion of pyrophosphate (an inhibitor of mineralisation) and 
other enzymes related to pyrophosphate metabolism in pulp 
and periodontal ligament suggested that mineralisation of 
cementum was more likely to be under the influence of the 
inhibitory effect of pyrophosphate than mineralisation of 
dentin. It has also been reported that dental effects of 
hypophosphatasia first diagnosed in primary teeth can also 
be seen in the permanent dentition.\textsuperscript{58} Both histological and 
radio logical changes, with a reduced level of marginal al veolar 
bone supporting the upper central incisors, large coronal pulp 
chambers in the molars, abnormal root cementum and dentin 
resorption and mineralisation disturbances have been ob-
served in a young man with hypophosphatasia.\textsuperscript{58}

It is clear that moderate forms of hypophosphatasia are 
highly variable in their clinical expression, owing in part to 
allelic heterogeneity but also to other factors that remain 
dertermined at this time. Nevertheless, the effect of this 
syndrome on the dentition remains one of the main diagnostic 
features and emphasises the critical role of the dental 
practitioner in treating this condition and the need for 
effective counselling of affected families.

2.6. Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a genetic disorder that occurs 
in approximately 1 in every 15,000 births and is caused by a 
dysfunction of the hypothalamus. PWS is now thought to 
occur through a lack of active genetic material in chromosome 
15.\textsuperscript{64} A deletion in part of this chromosome has been shown to 
occur in about 70% of patients, with another 30% or so of cases 
thought to occur through receiving both chromosomes from 
one parent rather than one from each parent.\textsuperscript{64} It affects males 
and females with equal frequency and all races and ethnic-
ties, and is recognised as the most common genetic cause of 
obesity. The main features of PWS include infantile hypotonia, 
mental retardation with behavioural abnormalities, develop-
mental delays, hypogonadism and marked obesity. Patients 
usually have a short stature, are obese with insatiable 
appetites and have small hands and feet with tapered digits. 
They often present with secondary symptoms such as 
diabetes, somnolescence, feeding difficulties, respiratory 
problems and scoliosis.\textsuperscript{65} The main orofacial features of 
patients with PWS are a narrow frontal lobe with almond-
shaped eyes often with up-slanting palpebral fissures, 
strabismus, triangular mouth and prominent forehead.\textsuperscript{66-68}

The major dental findings in PWS patients have been 
reported to be enamel hypoplasia and rampant caries with 
delayed eruptions and poor oral hygiene.\textsuperscript{54,66,67,69} Other 
features which have been reported include micrognathia, 
xerostomia, hypodontia and supernumerary teeth.\textsuperscript{69,70} Al-
though several studies have reported that the saliva in PWS 
patients is thick and sticky with a high viscosity and 
foaminess, no systematic investigations of salivary flow rate, 
buffering capacity or mineral content of saliva have been 
performed.\textsuperscript{67,68,70} Nevertheless it is likely that salivary 
dysfunction accounts for the high prevalence of caries, severe 
enamel loss and dental erosions. This coupled with consump-
tion of highly acidic drinks, occlusal parafunction and poor 
toothbrushing habits may predispose PWS patients to in-
creased tooth wear. Normal salivation has been shown to be 
critical in protecting teeth against the acidic factors that 
initiate dental erosion through its buffering capacity, clear-
ance by swallowing, pellicle formation, and remineralisation 
of demineralised enamel.

Since patient compliance may sometimes be an issue due 
to the mental and behavioural problems associated with 
PWS, dental treatment strategies may, through necessity, 
require a broad based approach to the issues of oral hygiene, 
diet, and care of teeth. In addition, the generalised caries 
which leads to almost complete destruction of the teeth may 
require a prolonged and extensive programme of treatment 
involving orthodontic, surgical and restorative proce-
dures.\textsuperscript{56,67}

2.7. Tricho-dento-osseous syndrome

Tricho-dento-osseous (TDO) syndrome is a rare, congenital, 
multisystem disorder belonging to a group of diseases called 
ectodermal dysplasias, which typically affect the hair, teeth, 
nails and/or skin and bones. TDO syndrome is characterised 
by kinky hair, thin and brittle nails, tooth enamel defects, 
increased thickening and/or denseness (sclerosis) of the 
calvaria and/or long bones of the arms and legs.\textsuperscript{71-73}

Individuals with TDO syndrome have been shown to 
exhibit several dental abnormalities that affect both the 
primary (deciduous) and secondary (permanent) teeth. Several 
studies have shown that both primary and secondary teeth of 
these patients can be abnormally prism-shaped with the 
majority of permanent teeth having an enlarged pulp chamber 
termed taurodontia.\textsuperscript{74-76} In addition, all the teeth from 
affected individuals exhibited some degree of decreased 
enamel thickness compared to control teeth ranging from 
no enamel to about 60% the thickness of normal teeth.\textsuperscript{75,76} In 
general, decreased enamel thickness was most severe in the 
primary teeth with a lesser degree seen in the secondary teeth. 
Light microscopy and electron microscopy studies of TDO 
teeth have shown pitting of the enamel surface, extensive 
enamel hypoplasia with no or limited prism formation. In 
contrast, dentine appeared structurally normal.\textsuperscript{75,76} Associat-
ed with the enamel hypoplasia, several studies have demon-
strated hypomineralisation with between 65 and 75% 
diminution in calcium (hypocalcification) and phosphorus in 
TDO enamel compared to controls.\textsuperscript{71,75,77} As a result, the tooth
enamel may be abnormally thin, soft, pitted and discoloured with short and open roots leaving the teeth highly prone to dental caries and infection. In some cases, affected individuals also exhibit widely-spaced teeth, absence of teeth, premature or delayed tooth eruption, or secondary teeth which become impacted in the gum. Many individuals lose their teeth early, typically in the second or third decade of life.71-73

Dental abnormalities associated with TDO syndrome may be detected using specialised procedures such as electron microscopy to reveal the extent of enamel hypoplasia and pitting within the enamel, and treated with a variety of techniques. Regular X-rays are important to monitor dental development with respect to premature or delayed tooth eruption, to detect impacted secondary teeth, and to help prevent, detect and/or treat other dental abnormalities. A variety of procedures may be used to restore improperly developed teeth to help prevent decay, abscess formation and/or tooth loss. Artificial teeth or other prosthetic devices may be used to replace lost or absent teeth, with dental surgery or other corrective techniques used to correct other dental abnormalities. Many of the dental abnormalities and other features associated with TDO probably occur as a result of a genetic defect at the molecular level in common developmental pathways for bone, teeth and hair. Spangler et al.75 have postulated that the life cycle or function of the ameloblasts may be particularly affected during the development of the primary and secondary dentition, accounting for the enamel hypoplasia and hypomineralisation seen in TDO patients. Certainly, this syndrome emphasises the need for a broad knowledge of the disease and its affects by dental practitioners and the requirement for further studies, particularly since the dental abnormalities appear to be the most consistent feature in TDO patients.73

2.8. Tuberous sclerosis

Tuberous sclerosis (TSC) is a rare genetic disease that causes benign tumours to grow in the brain and in other vital organs such as kidney, heart, eyes, lung and skin. It affects the nervous system and is associated with epilepsy, mental retardation, angiofibromas, along with skin and oral manifestations. The reported incidence of TSC ranges from 1 in 100,000 to 1 in 1,000,000 individuals, with a varied spectrum of symptoms and mild to severe disabilities.78

Several studies have investigated the incidence and extent of enamel pitting in TSC patients and have postulated that numbers of pits, particularly in permanent teeth, may be a helpful adjunct in diagnosing TSC.79-82 Mlynarczyk80 demonstrated 100% enamel pitting in the adult dentition of TSC patients compared to 7% of a control group using a dental swabbed onto dry teeth. In addition, patients compared to 7% of a control group demonstrated 100% enamel pitting in the adult dentition of TSC patients who were shown to carry the TSC gene.

In respect of the dental care of patients with TSC, mental retardation may lead to problems with patient compliance and necessitate the use of deep sedation or general anaesthetic to ease oral examination and evaluation.78 This in turn can lead to complications due to the presence in many TSC patients of pulmonary fibrous degeneration, kidney and cardiac lesions. In addition, the high incidence of enamel pits within this population may suggest a higher likelihood of caries development. Therefore periodic preventive measures, along with improved oral hygiene are important in the management and prognosis of these patients.

2.9. Familial steroid dehydrogenase deficiency

This condition arises from a rare autosomal recessive inherited liver disease caused by abnormal bile acid synthesis from cholesterol due to a deficiency in the enzyme 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase which leads to chronic liver disease in childhood as well as malabsorption of fats and fat soluble vitamins.84,85 Due to the rarity of this condition and the variability of the phenotype, only one study has reported on the incidence and extent of dental aberrations.86 This study showed an increased incidence of numerical (supernumerary) and structural (hypomineralisation and enamel hypoplasia) dental abnormalities linked to the presence of the autosomal inherited liver disease within first cousin-marriages in Saudi Arabia.86 Severe dental caries in combination with enamel hypoplasia with four supernumerary permanent tooth buds were observed in one subject at 4 years of age, which by 9 years had increased to 11, along with superficial enamel hypoplasia and general hypomineralisation. Treatment of the liver defect with large doses of chenodeoxycholic acid and Vitamin A did not account for the dental abnormalities, as treatment was started after the dental defects were diagnosed. The presence of supernumerary teeth may therefore result from the same genetic defect as the liver disease, with the observed enamel defects possibly resulting from either accumulating toxic cholesterol metabolites or deficiencies of fat soluble vitamins in early childhood.86 This condition represents a new association of dental defects with a genetically inherited syndrome.

2.10. Epidermolysis bullosa

Epidermolysis bullosa (EB) is a diverse, heterogeneous group of conditions characterised by fragility of the skin that results in blisters caused by little or no trauma.73,87,88 Three main types have been classified dependent on the histological level of tissue separation: epidermolysis bullosa simplex (EBS) is characterised by discontinuities in the epithelial keratinocyte layer, epidermolysis bullosa junctionalis (EBJ) is characterised by separation within the basement membrane, and, finally epidermolysis bullosa dystrophica (EBD) is characterised by discontinuities in the underlying connective tissue.87,88

The digestive mucosa, including the oral mucosa is one of the most frequently affected regions in this syndrome causing problems with feeding and marked oral fragility. In particular, junctional and dystrophic EB can be associated with marked
soft tissue scarring and alterations in the development of hard and soft tissues of the mouth.\textsuperscript{73,88}

The teeth of affected individuals have been shown to have thin enamel with localised or generalised enamel hypoplasia and defects such as pitting and furrowing, which in turn can predispose EB patients to an increased incidence of dental caries. Minor enamel defects have been shown to occur in all EB subtypes, with the most substantial occurring in the EBJ subgroup.\textsuperscript{57–90} All patients with EDJ have been reported to present with defects in enamel, whereas the prevalence of defects in EBS and EBD was similar to that of the control population (27%), suggesting that the mechanism causing damage to enamel may be very different between the three subtypes.\textsuperscript{86} In addition, Wright et al.\textsuperscript{88} reported that the incidence of dental caries was increased in patients with EBJ and EBD. Studies into the chemical composition of enamel from EB patients, in terms of mineral content, carbonate content, protein content and amino acid composition, have reported essentially normal enamel chemistry in EBD patients whereas EBJ enamel contained a significantly reduced mineral per volume content, which resulted in enamel hypoplasia.\textsuperscript{87,89} The high caries incidence in EBD patients may be related to other factors such as compromised oral hygiene, whereas in EBJ patients the enamel is developmentally compromised and associated with the genetic basis of the disease. In contrast, other workers have reported minor enamel defects in all three EB subtypes with a slight reduction (10%) in mineral content in some EBJ and EBD teeth.\textsuperscript{86} Overall no difference between mean mineral content of EB teeth and normal controls was observed, although marked alterations in the enamel structure, such as prismatic structure and orientation and surface pitting, was observed in EBJ teeth. It has been suggested that the genetic defect in EBJ accounted for the alterations in the structure of enamel whilst leaving the mineralisation process essentially intact. Given the systemic involvement of some EB subtypes, it is perhaps not surprising that some of the enamel defects seen in the three subtypes may be caused as a direct result of the molecular defect, whereas others are caused by mechanisms secondary to the disease process.

Due to the fragility of the oral mucosa and the increased susceptibility to dental caries, the dental management of these patients requires special care.\textsuperscript{73,97} Palliative and preventative treatment is important to prevent destruction and subsequent loss of dentition and may be sufficient for the majority of EB patients. More aggressive dental intervention and therapies may be necessary for the most severely affected patients to maintain oral health with frequent follow up visits and good hygiene and dietary advice essential.

2.11. Other developmental and environmental causes of enamel defects

Osteogenesis imperfecta (OI) is a relatively common inherited connective tissue disorder resulting in skeletal dysplasia and characterised by bone fragility and fractures. Other tissues including ligaments, tendons, facia, skin, eyes, ears and teeth, are also affected in OI. Most cases result from mutations in genes responsible for the production of type I collagen and the phenotypic presentation varies from mild to lethal. The most commonly observed dental abnormalities in OI include dentinogenesis imperfecta (DI) and malocclusion.\textsuperscript{92} DI, where teeth are discoloured, translucent and brittle, can occur in isolation as an autosomal dominant familial trait as well as a component of OA. Hereditary dentine disorders, DI and dentine dysplasia (DD), are characterised by abnormal dentine structure affecting either the primary, or both the primary and secondary, teeth.\textsuperscript{93} Currently DI has been divided into three subtypes, and DD into two. DI Type I is associated with OI, whereas type II is not. DI types II and III and DD type II are associated with mutations in dentine sialophosphoprotein (DSP),\textsuperscript{93,94} A recent study on Norwegian adults with OI found that they had twice as many missing teeth as the general population and higher numbers of endodontically treated teeth, although their daily oral health habits were good and they visited the dentist regularly.\textsuperscript{95}

Recommended treatment involves the removal of the sources of pain or infection, aesthetic improvement and protection of the posterior teeth from wear, using crowns, overdentures and dental implants. It is believed that where early diagnosis is made, and good treatment provided, excellent aesthetic and functional outcomes can be achieved.\textsuperscript{94}

The literature on amelogenesis imperfecta (AI) has been reviewed recently.\textsuperscript{96} AI primarily affects amelogenesis. The authors found that in case reports of AI aberrations were documented in the eruption process, crown morphology, pulp-dentine, and in the number of teeth. Additionally, calculus was commonly found, and gingival conditions and oral hygiene were often reported as poor.\textsuperscript{96}

Molar incisor hypomineralisation (MIH) is a common developmental condition resulting in enamel defects in the first permanent molars and incisors and presents at the eruption of those teeth. A rapid breakdown in the tooth structure may occur and therefore early diagnosis is important in limiting symptoms. Enamel hypomineralisation causes marked reduction in the elastic modulus of enamel, due primarily to an increase in the thickness of the protein layers between apatite crystals and, as a consequence, leads to impaired dental function.\textsuperscript{97} A recent review of the literature by Willmott et al.\textsuperscript{98} suggested that affected teeth indicated a systemic cause in the prenatal, perinatal or postnatal periods. At present the aetiology remains unclear, however, a number of possible causes have been suggested by several studies on children with MIH, including upper respiratory tract infections, asthma, pneumonia, otitis media, antibiotics, dioxins in maternal milk, tonsilitis and tonsillectomy, and exanthematous fevers of childhood.\textsuperscript{99–101} Many of these illnesses may produce hypoxia, hypocalcaemia or pyrexia in either the child or the mother.\textsuperscript{100} The reviewers concluded that there was little evidence to support any treatment option over another, with restorations using adhesive intra-coronal to extra-coronal restorations and, in severe cases, extractions of the first molars allowing the second molars to come forward, all proving effective. They did suggest that little improvement was achieved with microabrasion in anterior teeth, and that direct or indirect composite resin restorations may be appropriate in some children. It has been suggested that for children with repeated illnesses in the first years of life, and for those with opacities on erupted molars or incisors, it is useful to increase...
the frequency of dental check-ups during the period of erupting first permanent molars.\textsuperscript{102}

The possible environmental causes of enamel defects have been reviewed by Brook et al.\textsuperscript{2} by comparing an ancient (Romano-Briton) and modern British population. They used the same examiners and index and concluded that episodes of systemic illness and general debilitating factors can lead to enamel defects. In addition they reported that 68.4% of 1518 London schoolchildren had enamel defects in their permanent dentition, with 10.5% having 10 or more teeth affected, 67.2% with opacities and 14.6% with hypoplasia. A study in low birth weight children by the same authors showed significantly more enamel defects relating to major health problems, including mineral and vitamin deficiencies, low blood oxygen and ventilation requirement, occurring during the neonatal period.

Other factors which may cause enamel defects include cerebral palsy, mental retardation or hearing defects.\textsuperscript{103} Developmental hypoplastic enamel defects occur with greater frequency in the primary teeth of children with cerebral palsy, mental retardation or sensorineural conditions. This is in accordance with data from the study in children which showed that all the children with cerebral palsy had enamel defects.\textsuperscript{2} Many of the syndromes reported above are associated with features of mental retardation suggesting that mental conditions secondary to the syndrome itself may be the cause of some of the enamel defects observed. In children in particular, further research to ascertain whether the causes of dental defects occurred intra-utero, pre- or postnatally is required.

3. Conclusion

Enamel has a protective role on the tooth – loss of enamel exposes the sensitive dentine underneath. Once damaged, enamel is generally unable to recover. Enamel and dentine defects can present with a wide spectrum of clinical features and may be caused by a variety of factors occurring throughout tooth development from before birth to adulthood. These may include host traits, genetic factors, immunological responses to cariogenic bacteria, environmental and behavioural factors, and saliva composition. Tooth enamel and/or dentine are also affected by systemic diseases such as cystic fibrosis, HIV/AIDS, leukaemia, Alstrom syndrome, hypophosphatasia, Prader-Willi syndrome, Tricho-dento-osseous syndrome, tuberous sclerosis, familial steroid dehydrogenase deficiency and epidermolysis bullosa.

Systemic disease may arise from exogenous factors, including viral infections (e.g. HIV/AIDS), bacterial infections, and environmental factors (or stress) but can also be the result of endogenous genetic abnormalities (e.g. cystic fibrosis). The nature and severity of the disease itself as well as other factors often determine the extent of the damage to enamel and dentine. It is important for the dental practitioner to understand the nature of the underlying disease and the potential adverse effects that any therapy may incur.

A number of enamel and dentine defects occur as a result of the primary disease itself requiring the dental practitioner to have a broad based knowledge of the disease process and its effects in order to ensure the best possible dental care of the individual patient. The disease process, aetiology, patient’s current condition and relevant treatment strategies (especially with regards to immunosuppressed patients where the dental interventions themselves may potentially be life-threatening) will affect prognosis and must be carefully weighed before treatment plans are initiated.

The timing and nature of the stimuli which causes enamel defects may be very different between the various diseases or conditions; however the end result may be very similar as far as each individual patient and the dental practitioner is concerned.

In cystic fibrosis patients, for example, due to the increased prevalence of enamel defects and calculus accumulation, early dental intervention is important in the long-term care of these patients. Hypophosphatasia can present during the perinatal, infantile, childhood or adult stages. One of the main diagnostic features of hypophosphatasia, is the loss of dentition, probably due to the lack of cementum. Dental effects of hypophosphatasia first diagnosed in primary teeth are usually also evident in the permanent dentition, necessitating early dental intervention and counselling. Early long-term dental intervention is also important in individuals with Tricho-dento-osseous syndrome, where dental abnormalities affect both primary and secondary teeth, often resulting in the loss of dentition during the second or third decade of life. In Prader-Willi syndrome, a complex genetic multisystem sporadic disorder which presents during childhood and proceeds into adulthood, early dental consultation and long-term orthodontic, surgical and restorative procedures are usually necessary due to the almost complete destruction of the teeth which result from generalised caries.

It has been estimated that 30–80% of HIV/AIDS patients suffer with oral lesions, including fungal, bacterial or viral infections, neoplasms such as Kaposi’s sarcoma and non-specific presentations such as aphthous ulcerations and salivary gland disease. Although in many cases improved oral hygiene reduces and/or prevents oral disease, effective dental management remains an essential part of the overall care and health of HIV/AIDS patients. The need for improved oral hygiene is also an important aspect of the dental care of patients with tuberous sclerosis, a rare genetic disease that causes benign tumours to grow in the brain and in other vital organs, often associated with enamel pitting.

Many other systemic conditions, which have not been discussed in detail here, are known to affect enamel. The hypocalcification type of Amelogenesis imperfecta, an autosomal dominant condition, results in incomplete enamel mineralisation. The X-linked hypoplastic type on the other hand results in enamel hypoplasia, which is nevertheless of normal composition. Chronic bilirubin encephalopathy may also cause enamel hypoplasia and green staining of the enamel. Erythropoietic porphyria results in porphyrin deposition in the body including in tooth enamel where the deposits appear red and fluorescent). Celiac disease results in enamel demineralisation.

Many difficulties arise from the variety of terminology and indices used to measure dental damage often making comparisons between different studies difficult, adding to the complexities of assessment and treatment. Nevertheless,
the availability of many new technologies in dental management, restorative care and assessment now make treatment of individual patients both more rewarding and complete than previously possible.

REFERENCES


