Universidad Europea

TRABAJO DE FIN DE GRADO

Grado en Odontología

DENTAL ENAMEL

INTEGRATING MINERAL CHEMISTRY, BIOCHEMISTRY, CELL BIOLOGY AND GENETICS

Madrid, curso 2020/2021

Número identificativo **247**

SUMMARY:

Objectives: The main objective of this study was to analyse the composition of the dental enamel in its complete form regarding mineral chemistry, biochemistry, cell biology and genetics. This objective was achieved by integrating all this scientific fields to dental enamel and thanks to this high-mineralized tissue, scientists have been able to perform a huge amount of studies and for many reasons; it is represented as an exemplary model for biological, biochemical, and mineral and genetics studies.

Methodology and results: An extensive bibliographic review has been carried out in the CRAI-Library UEM using numerous scientific articles in English from 2010 to 2020, including these following keywords as: genetics, biochemistry, biology, mineral chemistry, dental enamel, amelogenesis, mineral structure and excluding terms such as dentin, pulp**...**

Conclusion: Thanks to scientific researchers that allowed and provided us a huge amount of details around dental enamel properties and thanks to scientific development that has an important part to play in populations and health. During the ten past decade, science have been improving and increasing so much that all details brought around dental enamel permitted an integration of mineral chemistry, biology, biochemistry and genetics to dental enamel.

RESUMEN :

Objetivos: El objetivo principal de este estudio fue analizar la composición del esmalte dental en su forma completa en cuanto a química mineral, bioquímica, biología celular y genética. Este objetivo se logró al integrar todos estos campos científicos al esmalte dental y gracias a este tejido altamente mineralizado, los científicos han podido realizar una gran cantidad de estudios y por muchas razones; se representa como un modelo ejemplar para estudios biológicos, bioquímicos, minerales y genéticos.

Metodología y resultados: Se ha realizado una extensa revisión bibliográfica en la CRAI-Library UEM utilizando numerosos artículos científicos en inglés de 2010 a 2020, incluyendo las siguientes palabras clave como: genética, bioquímica, biología, química mineral, esmalte dental, amelogénesis, mineral. estructura y excluyendo términos como dentina, pulpa ...

Conclusión: Gracias a los investigadores científicos que nos permitieron y nos brindaron una gran cantidad de detalles sobre las propiedades del esmalte dental y gracias al desarrollo científico que es fundamental en nuestra vida diaria. Durante la última década, la ciencia ha ido mejorando y aumentando tanto que todos los detalles introducidos en el esmalte dental permitieron una integración de la química mineral, la biología, la bioquímica y la genética en el esmalte dental.

TABLE OF CONTENTS

1. INTRODUCTION:

1.1. Thesis structure:

The thesis has been organised such as the introduction has been outlined in the first part. This one provides a basic examination around dental enamel structure and composition. Then, general aims and objectives have been outlined in part 2. The fourth part will be results classified by a table determining the type of article founds, and then discussion follows. The last part will provide a conclusion.

1.2 INTRODUCTION TO ENAMEL:

1.2.1 Basic tooth structure:

The tooth is composed of three major layers: Enamel, Dentin, and Pulp (Figure 1)(1). Enamel is a translucent substance that constitutes the outer part of the crown of the teeth and which covers dentin. It acts as a barrier to highly protect the tooth from external substances as sugar, acid drinks and other threats….(2)

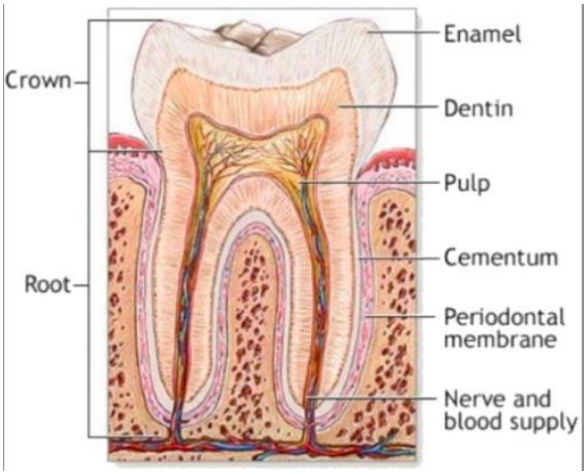


Figure 1. *Image showing a schematic drawing of a tooth*.(3)

1.2.2 Enamel:

It is the hardest and the most mineralized structure in the human body(4). In addition, enamel is one of the four main components that build up the tooth along with dentin, cement and the dental pulp. It is a visible dental structure, supported by an underlying layer of dentin that cannot be related to tissue because it is not vascularized nor innervated, and in fact it is mineralized(5). Enamel is a mineralized cell-free tissue protecting the pulp-dentin complex. Its thickness varies from 2.5 mm opposite the cusps, to become more refined at the level of the neck but also at the level of the cement-enamel junction.(6) The enamel is composed of 96% mineral matter, and the rest is water and organic matter(7). The mineral part is mainly constituted by a network of calcium hydroxyapatite crystals which crystallize in the hexagonal crystal system(1). These crystals that are found in the enamel are about 25 times larger than those found in dentin. Crystal size is a very important factor in the extreme hardness of enamel, in contrast to dentin. The high mineral percentage is not only responsible for its hardness or strength, but also for its friability. On another hand, Dentin, which is less mineralized, is essential as a support and compensates for the weaknesses of the enamel (8). For a long time it was thought that enamel was a complex chemical system, but it did not have much dynamics. Today we know that enamel participates in many processes such as: Ions transport from saliva to dentin (crosses the enamel and could modify its structure) or ion exchange reactions with the responsible saliva phenomena of demineralization and remineralisation(9). Enamel is not an inert system at all. When we look at the ultra-structural and therefore nano-structural level, we see that it is a unique self-assembly in the mineral world (acellular, avascular and non-innervated enamel).(9) Enamel is the hardest and most densified structure in the body. Dental enamel is an example of

organic material that unites at the same time mineral chemistry, biochemistry, cell biology and genetics(10). The environment and enamel's hereditary defects can induce destruction, degradation or enamel malformations(11). Unlike most other biological mineralized biological tissues, the enamel is not able of regeneration process due to the loss of cell forming known as: Ameloblasts(10). The interface between physics, chemistry, and genetics has been initiated for a long time and shown a huge world around dental enamel properties.(10)

2. General aims and objectives:

The general aim of this study was to understand the complexity of the dental enamel integrating the knowledge about its mineral chemistry, biochemistry, cell biology and genetics.

3. Material and methods:

A search was conducted in CRAI-Library UEM, PubMed, and Medline using many scientific articles in relation to our main objectives. A selective research has been made using the filter: “Refine your research” so that our final project fulfils our objectives. First and foremost terms as: Dental enamel, mineral chemistry, biochemistry, biology and genetics have been included in our research. Secondly terms as mammalian, dentin or pulp has been excluded. Our Scientifics articles have been searched in the category (Full text document) by limiting the publishing date from 2010 to 2020 using English language. Once the results were obtained, all those articles that after reading it were considered none useful information for the present bibliographic review were eliminated, either due to an incorrect use of the term "integrating" or because they did not delve into the issues concerning the objectives of this work. The bibliographies of the most relevant articles were also analysed and sourced, this way only the most significant information was chosen for this work.

4. Results:

More than 40 scientific articles were selected in order to conduct our study where the main purpose was to analyse the enamel properties integrating mineral chemistry, biochemistry, biology and genetics. The majority of these scientific articles are related to enamel properties, others to chemical and biological characteristics, a group of articles to its development process according to genetic and others according to demineralisation/remineralisation process.

DENTAL ENAMEL INTEGRATING MINERAL CHEMISTRY, BIOCHEMISTRY, CELL BIOLOGY AND GENETICS	
	ACCORDING TO BIBLIOGRAPHY
GENERAL DENTAL ENAMEL COMPOSITION AND PROPERTIES	(1) , (4) ,(6) ,(7) , (8) , (9) , (10) , (13) , (15), (16) , (17) , (18) , (19) , (20) , (21) , (22) , (25), (29) , (30) , (31) , (32).
INTEGRATING MINERAL CHEMISTRY	(1), (2) , (5) , (7) , (9) , (12) , (13) , (14) , (15), (16) , (18) , (19) , (20) , (22) , (30) , (31) , (32) , (33) , (34) , (39) , (40) , (42), (43) (44) , (46),
INTEGRATING BIOCHEMISTRY AND CELL BIOLOGY	(1) , (3) , (9) , (11) , (12) , (13) (15) , (16) , (19) , (20) , (21) , (30) , (32)

INTEGRATING GENETICS	(1), (6) , (8) , (9) , (10) , (13) , (15) , (16) , (20), (23) , (24) , (25) , (26) , (27) (28) ,(29) , (30) , (31) , (32) , (35) , (36) , (37) , (38).

Table 1: Table showing the repartition of each article according its principal characteristic.

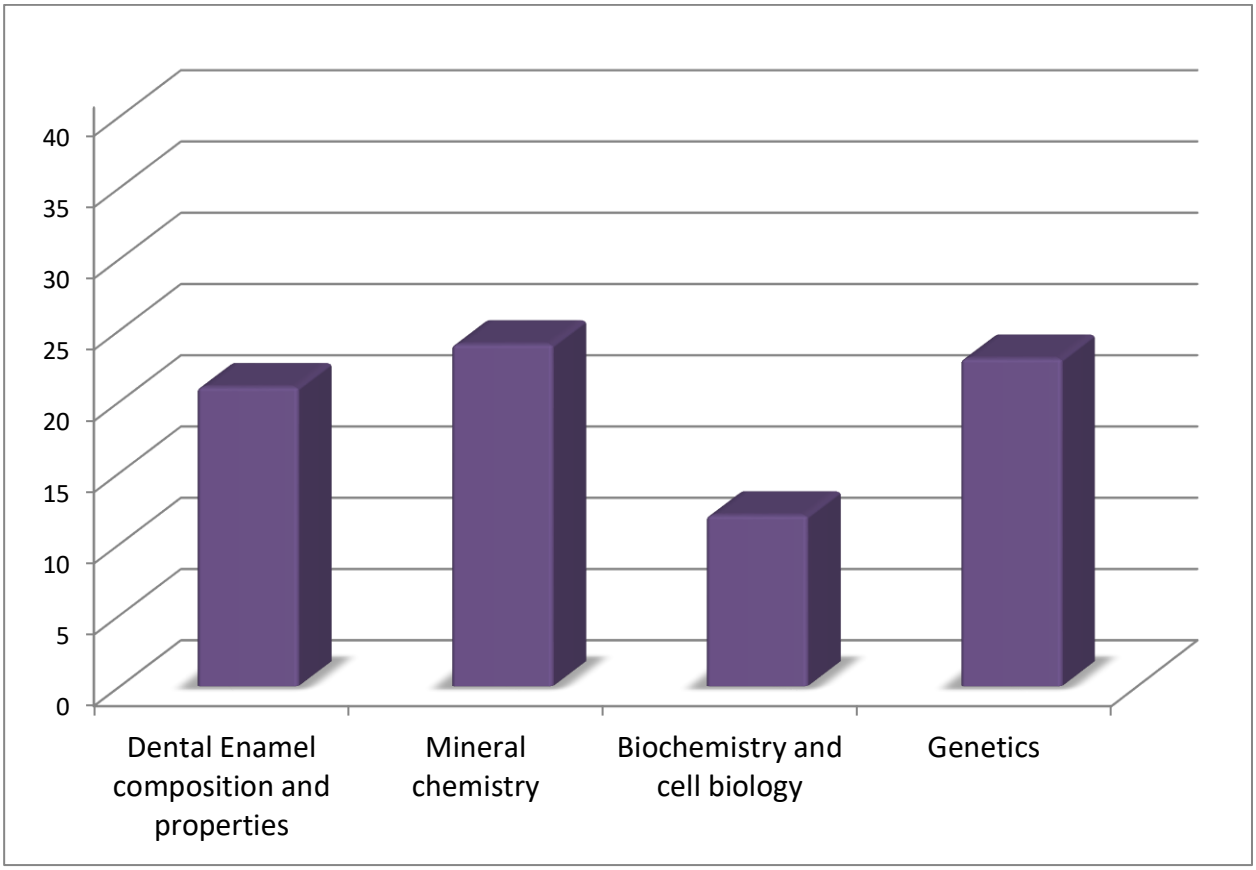


Table 2. Table showing the articles proportion according to its principal theme.

5. Discussion:

5.1 Hydroxyapatite crystal structure:

Dental enamel is the most mineralized and strongest material in the human body with a total of 96% of inorganic matter presented in form of mineral crystal(12). The main mineral content of dental enamel is a non- stoichiometric calcium deficient carbonated hydroxyapatite (HA) [Ca10(PO4)6(OH)2](13). HA is part of the calcium phosphate group, which also have octacalcium phosphate (OCP), a precursor phase of HA and tricalcium phosphate (TCP). Each unit cell of a hydroxyapatite crystallite has a central hydroxyl group with by three calcium ions which are surrounded by three phosphate ions(2). The union of six calcium ions makes a hexagonal form due to its enclosure.)(1).

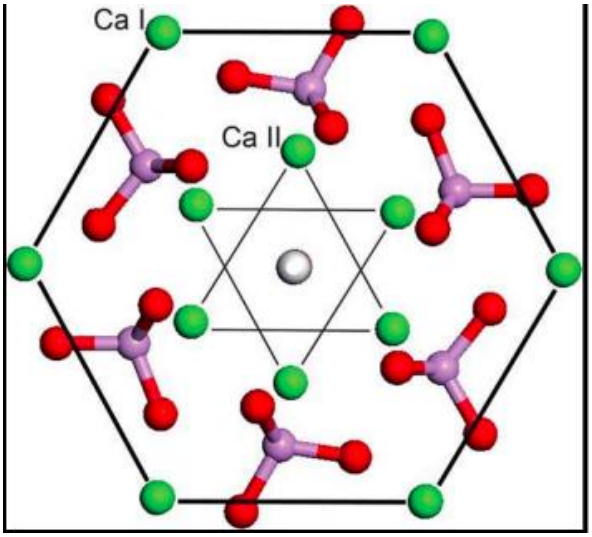


Figure 2.*Image showing a diagram of the unit cell of a hydroxyapatite crystallite****.(2)***

Each atomic site in the HA crystal may include some substitutions: For example the Ca site in the apatite structure can be replaced by metal cations, e.g. Na, K, Mg, Sr, Ba, Mn and Pb ,

carbonate may substitute phosphate or hydroxyl ions .All these substitutions depend on local carbon dioxide concentrations which occur during tooth development. Substitutions have negative aspects, which receive the name of distortions, and they affect the apatite solubility, which is an important factor to consider during the dental demineralization(14). The crystallographic unit cell stoichiometry is made up of four columnar calcium II ions, six screw axis calcium I and six phosphates located around the hydroxyls, which occupy columns on the screw axes. Its structure consists of mirror planes at z= ¼ and ¾ (1).

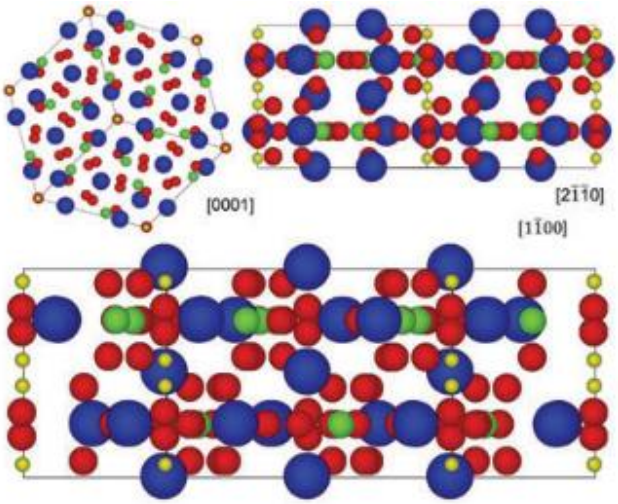


Figure 3. *Schematic projection of the hydroxyapatite's hexagonal structure in the [0001], [2–1-10] and [1–100] axes, respectively.*

(Ca2+ =blue, P= green, O= red and H= yellow). (Mg2+)(RMg2+.

Image taken from Crystallographic structure of human tooth enamel (15)

5.2 Enamel microstructure:

In enamel microstructure, heterogeneity exists due to the variation in the orientation of prisms and the crystallites. In the apex/cusp regions of the tooth, the orientation of the

crystallites is parallel with the direction of the prisms perpendicular to natural biting surfaces(15). However, in the lateral enamel, crystallite direction is oriented far from the prism axes towards the cervical margin. Deciduous enamel has less well-structured crystal arrangement than permanent enamel, although prisms are smaller, the crystallites within them are larger.(15)

The unique structure of the enamel responds to a highly organized architecture giving it its hardness and great resistance to masticatory forces. Two types of enamel can be distinguished according to their histological characteristics: prismatic enamel and aprismatic enamel.(16)

5.2.1 Prismatic enamel:

Enamel is made of single crystals of hydroxyapatite. They represent the smallest identifiable structural unit within the enamel (nanostructure of approximately 10 angstroms) and their assembly gives rise to crystallites with a hexagonal section 50 times greater than that of single crystals (microstructure of 500 angstroms). These crystallites will themselves interlock to form the enamel prisms (3 micron section).(17)

We then dissociate two types of enamel according to the orientation of the crystallites: Prismatic enamel: the crystallites are oriented parallel to the major axis of the prism.(17)

Inter-prismatic enamel: crystallites adopt an angle of about 60 ° (regarding the major axis of the prisms). In the longitudinal section, the inter-prismatic substance covers the prisms on both sides. In the cross section, the inter-prismatic enamel covers them completely or partially, except at their base where the two structures are one. (18)

5.2.2 Non prismatic-enamel:

On another hand, this type of enamel is simply made up of crystallites and remains devoid of this histological feature (prisms). It is observed on either side of the prismatic enamel, thus forming an internal non-prismatic enamel (opposite the enamel-dentin junction) and external (coronary surface), extending over approximately 30 microns.(17) This structural difference is explained by the different stages of amelogenesis. The pre-secretory ameloblasts are at the origin of the first apposition of non-prismatic enamel next to the dentin, thus participating in the formation of the enamel-dentin junction.(16) Subsequently, the placement of the interprismatic enamel (by the secretory ameloblasts this time, an extension of Tomes) makes it possible to constitute a lattice, which will be colonized by the prismatic formations. The thin layer formation of external aprismatic enamel corresponds, for its part, to a post-secretory maturation phase.(18)

Figure 4. *Image showing prismatic and interprismatic enamel, different crystal orientation*(18)

5.3 Enamel chemistry:

Enamel, although devoid of cells, is not inert and ionic exchanges are perpetually made between the enamel surface and the oral environment. The inter-prismatic substance with a higher aqueous and organic content than enamel prismatic is the privileged place of these exchanges.(19) These interactions are largely determined by oral ph. In the case of acidity, the hydroxyapatite crystals forming the enamel matrix are dissolved and the phosphate / calcium released within the oral cavity. On an opposite side, in the presence of an alkaline pH, they are able to precipitate in contact with the enamel.(15) It is important to know that fluoride ions are essential to fight against acid attacks. Integrated into the hydroxyapatite, the resulting fluoroapatite crystals are more chemically stable, more symmetrical and therefore ultimately more resistant. The mineral component of enamel consists in a basic replacement of calcium hydroxyapatite, the stoichiometric formula for hydroxyapatite (HAP) being *(Ca10 (PO4)6 (OH)2*)(12). Within enamel a number of ions can be missing from HAP and different elemental substitutions can exist within the HAP, for examples, calcium replaced by sodium, magnesium, zinc… carbonate replacing phosphate, and fluoride replacing hydroxyl(20). These defects and substitutions can impact the behaviour of HAP, especially to its solubility at a lower ph.

5.3.1 Mineral phase:

It represents 96% of the enamel mass, or 87% of the volume. It is formed by major elements, such as: calcium, phosphate, carbonates, sodium, magnesium, chlorine and potassium. Minor elements such as fluorine, strontium, zinc… are also found. These can come from

environmental contamination.(21) Apatite crystal has two properties: it allows ionic exchange and can also absorb ions on its crystal and thus give crystals of hydroxyapatites, fluoroapatites, carbonatoapatites ...(16)

5.3.2 Organic phase:

The organic phase represents 0.6 to 1% of the tissue weight in mature enamel. It is composed of residual non-amelogenin proteins and phospholipids. Proteins are mainly glycoproteins different from keratin. It is made up of different proteins detailed below:

- *Amelogenins*, which are hydrophobic proteins that disappear with enamel maturation and are replaced by hydroxyapatite crystals. They are distinguished by their composition rich in amino acids (proline, glutamine, leucine and histidine) and are involved in the control and direction of crystal growth.(16)
- *Enamelins*, which are phosphoproteins rich in glutamic and aspartic acids, serine and glycine. They persist in mature enamel tissue and are located on the surface of crystals.(16)
- *Tuftelins*, which are acidic proteins in enamel that belong to the enameline family. They are particularly rich in glutamic and aspartic acids.(16)The organic matrix also includes lipids: cholesterol, phospholipids and triglycerides.(17)

5.3.3 Aqueous phase:

Water is present in enamel in a free form (1% of tissue weight) or in a bound form (2.4% of tissue weight).(16) Water is mostly found in inter-crystalline spaces and it contributes to the

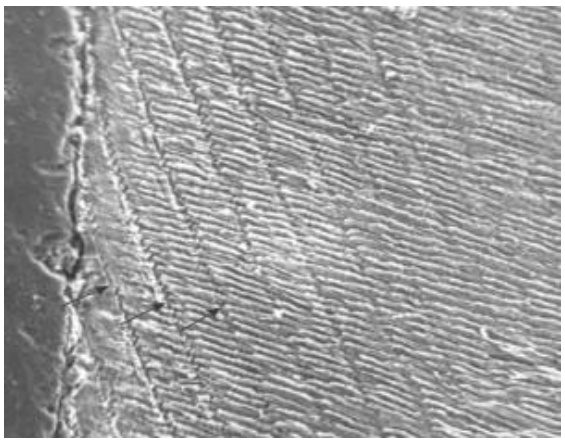
formation of a protein shell around the crystallites. This hydrated matrix is essential for ionic exchanges and diffusions.(18)

5.4 Enamel Histology:

On a microscopic scale, other particular structures need to be individualized: the Retzius striae and the Hunter-Schreger bands. These secondary formations allow the enamel to adapt to the masticatory forces in a remarkable way.(18)

5.4.1 Retzius striae:

Retzius striae or lines correspond to demarcation between two successive cycles of enamel application. Spaced evenly, they are identifiable every 25 microns. Their characteristic appearance in concentric formations makes it possible to assimilate them to the structure of a tree trunk, witness of cyclical growth. On the surface of the enamel, these striations undergo a slight inflection and form furrows called "perikymatias" which tend to disappear with the natural wear of the teeth.(17)



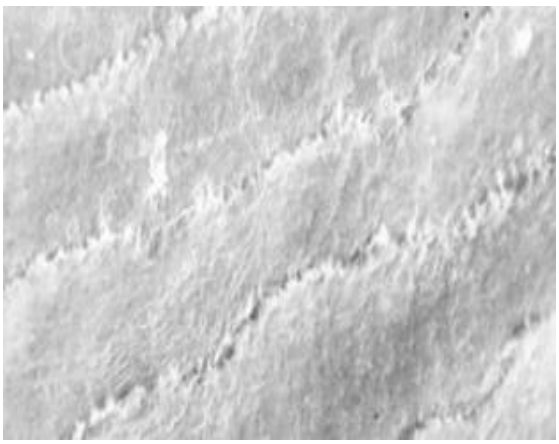


Figure 5. *Image showing Retzius striae (indicated by arrows) on the left side.* (22)
Figure 6. *Image showing Perikymatis on the surface of the enamel on the right side.*(22)

5.4.2 Hunter-Schreger bands:

The orientation of the enamel prisms is not uniform throughout its thickness. Initially orthogonal to the surface, they undergo a change of orientation (approximately 2 to 3 °) with each crossing of a Retzius striaes, in the direction of the enamel-dentin junction. This is materialized under the microscope by the alternation of light bands (= parazonia) and dark bands (= diazonia), called Hunter-Schreger bands.(23) When studying an enamel section, the prisms sectioned transversely as to their axis will be more easily demineralized by acid dyes and therefore give rise to dark bands (because they are colored). Conversely, the longitudinally sectioned prisms will be less sensitive to acid dyes due to their orientation and thus form the light bands.(24)

Figure 7. *Hunter-Schreger bands where we can see the alternation between light bands and dark bands.*(22)

5.5 Enamel Cell Biology:

5.5.1 Dental germ formation:

In humans, the development of teeth results from a biological interaction of two cell groups resulting from the ectoderm and ectomesenchyme. Indeed, each dental organ is the result of cellular morphogenic movements and the cooperation of epithelial and mesenchymal protagonists.(25) Dental germs will pass successively through the blade, bud, cup and, finally, bell stages depending on the degree of differentiation of their epithelial cells. It is at the bell stage that the mineralized tissues of the tooth (enamel) will be developed. Once the morphogenesis and mineralization of the crown is complete, we will see rhizagenesis, development of the supporting tissues of the tooth and finally dental eruption.(6)

- A BUD STAGE
- B CUP STAGE
- C BELL STAGE
- D AND E AMELOGENESIS
- F CROWN FORMATION
- G RHIZOGENESIS AND ERUPTION
- H TOOTH

Figure 8*. Image showing the steps of tooth development.*(18)

5.5.2 Bud stage:

From the dental blade, ten buds will individualize per arch from the 7th week of intrauterine life. The dental lamina will partially involute, epithelial islands will persist to ensure the morphogenesis of the permanent teeth, the permanent molars developing from distal extensions (molar lamina) of the dental lamina of the premolars.(25)

5.5.3 Cap stage:

The proliferation of cells from the bud causes the germ to pass through cup stage. At this stage, we can highlight: - an epithelial component at the origin of the enamel - an ectomesenchymal component at the origin of the primitive papilla - and around this set, an ectomesenchymal condensation at the origin of the follicle fibrous.(26)

5.5.4 Bell stage:

The bell stage is that of histodifferentiation and morphogenesis. At this stage, the tooth germ is made up of the enamel organ, the primary dental papilla and the follicular sac.(27)

- *The external epithelium: The* cells of the outer adamantine epithelium form a row of cubic cells joined together by hemi desmosomes and communicating junctions. They are located at the periphery, separated from the follicular sac by a basement membrane. (18) They do not participate in the formation of the enamel itself, but have a function of internalizing precursors from the capillaries that surround the organ of the enamel.(22)

- *The stellate reticulum: the* stellate-shaped cells delimited between the outer adamantine epithelium and the intermediate stratum produces it formation. (18) The cells in fact connected to each other as well as to the intermediate stratum cells by intercellular junctions such as mosomes and communicating junctions. However, the intercellular space remains important. Large spaces of interstitial fluid rich in glycosaminoglycans and lipids separate cells from each other. This organization allows the diffusion of precursors and nutrients first and secondly the formation of a hydrostatic cushion protecting the internal adamantine epithelium from external pressures.(8)
- *The intermediate stratum:* It is made up of one or two rows of cubic or squamous cells attached to the internal adamantine epithelium cells to which they are connected by desmosomes and communicating junctions. These cells provide glycogen, an essential element for the energy supply allowing all transfers in the enamel organ.(18)
- *The internal epithelium:* The internal epithelium cells lie on the basal lamina that separates them from the primary papilla. In the bell stage the internal epithelium cells have a similar structure to the external adamantine epithelium, their shape is slightly more elongated.(25) The differentiation of this epithelium occurs under the influence of the primitive papilla. The cells will first become pre-ameloblasts, then pre-secretory ameloblasts, and finally secretors, which are involved in the establishment of the enamel matrix. There is a junction zone between the internal and external epithelium, called the reflection zone. These cells multiply actively and cause the growth of the enamel organ.(28)

5.6 Enamel Genetics:

5.6.1 Dental enamel formation: reminding:

Amelogenesis is by definition enamel formation process(12). During the crown stage of development, enamel forming cells: ameloblasts, secrete a protein rich matrix during the Secretory stage which is followed by a degradation due to a proteolytic enzymes and is then replaced by hydroxyapatite during the Maturation stage(2). The internal enamel epithelial cell goes through many morphological changes during enamel formation. The first stage is the presecretory stage, which is characterised by columnar cells; They have a reversal of polarity whereby the nucleus moves to the stratum intermedium end of the cell(1). The dental lamina rapidly folds and penetrates the underlying mesenchyme to form the dental placode, followed by the bud, cap, and bell stages(27). All these stages shape the crown, and then are followed by the root's development. The mesenchyme immediately underlying the dental epithelium is derived from cranial neural crest cells(29). Very early in tooth formation there is epithelial-mesenchymal molecular cross- talk initially orchestrated by the mesenchyme, such that epithelial cells destined to create enamel start to differenti- ate to form ameloblasts, and the underlying neural crest- derived mesenchyme differentiates into cells that will form the remainder of the tooth(6).

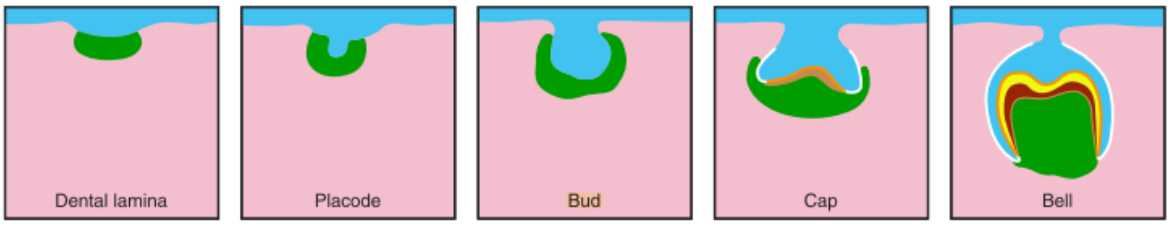


Figure 9: *The principal stages of tooth formation.(6)*

5.6.2 Amelogenesis:

Amelogenesis is enamel formation with an ectodermal origin.(18)The ameloblasts that are responsible for amelogenesis arise from the differentiation of cells in the internal dental epithelium of the enamel. Human enamel is formed at a rate of approximately 4 µm per day, starting at the future location of the cusps of the tooth (enamel node; Figure 1) around the 3rd or 4th month of pregnancy.(30)

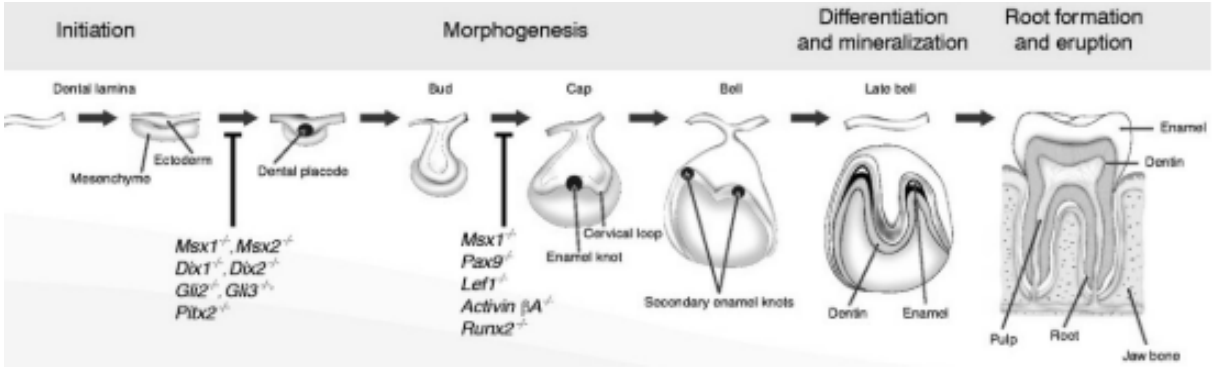


Figure 10. *Image showing steps of odontogenesis process.*(30)

5.6.2.1 Ameloblasts:

- *Pre-secretory ameloblast*: During the pre-secretion period, the tooth acquires its shape (morphogenesis). Coming out of its mitotic cycle, the pre-secretory ameloblast differentiates and develops the elements necessary for protein synthesis and secretion. This stage was classically seen as a period during which the ameloblast is preparing to enter an intense phase of production.(22)

However, it has been shown that these pre-ameloblasts already begin to secrete enamel proteins. The pre-ameloblasts constitute an internal adamantine epithelium at the internal border of the enamel organ. In this vascularized organ, three cellular layers are observed

from the outside to the inside: the external epithelium, the stellate reticulum and the intermediate reticulum.(18)

- *Secretory ameloblast*: Also called a functional ameloblast, it develops, during the following stage, at its apical part a cellular extension, the extension of Tomes. During this stage, the entire enamel layer is formed. (10)The complex organization of the enamel is due to the arrangement, orientation of the extension and the displacement of the ameloblasts on the surface of the forming crown. Ameloblasts have two secretion sites. The enamel crystallites organize themselves into interprismatic enamel or rods (or prisms) depending on where the matrix is secreted. The distal part of the extension of Tomes is involved in the formation of rods while the proximal part is responsible for the formation of interprismatic enamel against a single necessary for the rods. Ameloblasts secrete constitutively, that is to say continuously.(28)

- *Post-secretory ameloblast*: Most of the previously secreted organic matrix is enzymatically degraded and eliminated during maturation. This biochemical mechanism allows the growth in width and thickness of crystallites.(18) During this stage, the post-secretory ameloblasts become shorter and wider. The ameloblasts stop secreting and regress once the enamel is fully mature. This is called a “reduced” enamel organ that isolates the enamel from the neighbouring connective tissue.(30) Thus, amelogenesis takes place in three stages, we distinguish the cyto-differentiation of ameloblasts, the secretion of the enamel matrix, and the mineralization and maturation of the enamel.We will describe these different steps, as well as the genetic regulation and the role of enamel proteins in the process of amelogenesis.

5.6.2.2 Amelogenesis steps:

- *Ameloblasts cytodifferentiation*: During cytodifferentiation, cells differentiate and become functional. It is also observed the resorption of the basal lamina between the internal adamantine epithelium and the primary papilla.(31) At the end of the bell stage, the internal adamantine epithelium is made up of a layer of cells called preameloblasts. Preameloblasts are cells with a programmed number of mitoses, at their last division they become presecretory ameloblasts. During this phase, the tooth acquires its shape, and the ameloblast prepares to enter a phase of secretion. The presecretor ameloblasts are post-mitotic cells, aligned in a palisade that rest on a basal lamina which foreshadows the future enamel-dentin junction.(18) They develop organelles involved in protein synthesis and secretion. Studies have shown that the presecretory ameloblast already participates in the synthesis of enamel proteins but not yet in the formation of the first enamel layer.(18) These elongated cells measure 70 µm in height and approximately 3 µm in diameter. As seen previously, the nucleus is basal, the Golgi apparatus supranuclear, the endoplasmic reticulum is poorly developed, but the number of cisterns is increasing. We see many lysosomes appear. The desmosomes and communicating junctions, which unite these cells apically, will be reinforced by the formation of tight tight junctions. The presecretory ameloblasts then form a sealed cell compartment.(18)

The basal lamina fragments and becomes discontinuous. The apical end of the presecretory ameloblasts changes and exhibits numerous evaginations. Indeed, this differentiation is the consequence of interaction between epithelial cells and peripheral fibroblasts of the mesenchymal papilla.

- *Secretion of the enamel matrix*: The cells then goes to the secretory ameloblast stage, which is functional. During this phase, the ameloblast actively secretes the various matrix proteins. The entire layer of enamel will be formed and the secretory ameloblast is a prismatic cell 70 µm high.(30) Its basal third is rich in mitochondria and contains the nucleus. This region does not show much change compared to the previous stage, it is still connected to the cells of the intermediate stratum and ensures the transfer of precursors. (18) Its central part, called supra nuclear, includes the endoplasmic reticulum and the Golgi apparatus, the latter is long (50 µm) and extends to the apical part where it releases its secretory vesicles.(22) The transition from presecretory ameloblasts to secretory ameloblasts is gradual. So before the extension of Tomes appears, a first layer of enamel is deposited on a dentin, which has become compact. This initial layer of enamel is aprismatic and measures 10 µm thick. It forms the enamel-dentin junction. The cells of the stellate reticulum disappear by apoptosis, bringing together the cells of the outer adamantine epithelium and those of the stratum intermedium, which together form the papillary layer. This phenomenon is important since it brings the vascularization of the fibrous follicle closer to the ameloblasts. (8)This vascularization now represents the only nutritional contribution, because the mineralized layers prevent a supply from the pulp. As the extension of Tomes develops at the apical pole of the cell, the immature prismatic enamel will be deposited. Its complex organization is due in part to the orientation of the extension and the displacement of the ameloblasts on the surface of the developing crown. The enamel secretion will take place in two successive stages: lateral secretion first, on either side of the extension of Tomes, an interprismatic enamel network is set up. (18)Then in a second step, the cubicles occupied by this extension will be filled with intraprismatic enamel. There is no difference in

the composition of the organic matrix or the crystalline phase between the two types of enamel. Several ameloblasts are involved in the development of interprismatic enamel, while intraprismatic enamel is secreted only by an ameloblast. The migration of ameloblasts causes the extension of Tomes to stretch. This will gradually disappear. The last layer of enamel put in place will again be aprismatic.(18)

- *Mineralization and maturation of enamel*: During the secretion phase, transient young enamel is put in place. The organic matrix of this enamel is 90% amelogenin. It also contains ameloblastin and enameline, as well as other minor enamel proteins such as tuftelin. These proteins as well as their role will be described below. The mineralization and maturation of the enamel therefore consist of a growth in thickness and width of the crystallites, this being possible by the degradation of the organic matrix and by the massive influx of calcium and phosphate ions. Half of the ameloblasts will die by apoptosis. Post-secretory ameloblasts spend 80% of their life as a folded cell. There is a coupling between the apical pole aspect and the junction systems between cells. Indeed junction complexes can go from a tight organization to a non-tight organization. When the cell has a wrinkled appearance, it will have tight junctions at the apical level and looser (permeable) junctions at the basal level, and vice versa for smooth-looking cells. The modulation phenomenon would allow: the elimination of protein fragments, the balance between acidity and neutrality of immature enamel and finally the supply of calcium necessary for the growth of crystallites. Indeed, the folded cells will internalize the peptide residues resulting from the degradation of the enamel matrix and thus they will complete their degradation. On the other hand, the ameloblasts with a wrinkled appearance will initially secrete protons causing acidification of the medium. This acidity is essential for the proper functioning of two enzymes secreted by

these same ameloblasts: MMP-20 (an enzyme from the metallo-protease family) and a serine protease also called kallikrein-4. As the enzymatic activity is optimal, the enzymes will be able to degrade the enamel proteins.

However, the drop in pH would lead to the dissolution of the crystallites. The folded cells participate in the neutralization of the pH, in a second step, by the secretion of bicarbonate ions. Smooth-rimmed cells are also involved, allowing interstitial fluid to pass through immature enamel through their loose junctions. The pH being neutralized, the crystallites will be able to grow. Finally, modulation plays an important role in the acquisition of the calcium necessary for the growth of crystallites. Calcium comes from the interstitial fluid (from the bloodstream of the tooth follicle). The latter will be able to enter the enamel by passing between the cells with smooth edges thanks to their non-waterproof junction complex. Cells with a folded border are also actively involved in calcium transport. These cells contain membrane calcium ATPases that allow the incorporation of calcium into the matrix of the enamel being formed. Mature enamel is composed of an average of 96% crystals, 3.2% water and 0.8% organic matter. When maturation is complete, the ameloblasts stop modulating and regress, they become protective ameloblasts. These will merge with the papillary layer and together form the reduced adamantine epithelium. Its role is to isolate the enamel from the surrounding connective tissue until the tooth has erupted. When the tooth hits the arch, part of the reduced enamel organ participates in the formation of the junction structures that connect the periodontium to tooth.

5.6.3 Amelogenesis imperfecta:

Amelogenesis imperfecta is an inherent disease that is represented by qualitative or quantitative enamel defect in the absence of systemic complication(32). Hereditary brown enamel, hereditary enamel dysplasia, hereditary brown opalescent teeth are the other terminologies used for AI. The prevalence varies from 1:700 to 1:14 000, according to the studies done to the population. Amelogenesis imperfecta affects the whole ectodermal component and it can be either autosomal dominant, recessive or X- linked mode of inheritance(33). This malformation affects both dentitions: primary and permanent. In the teeth affected by AI, the dentin and roots have a normal shape. In relation to the phenotypic characteristics and mode of inheritance, AI is divided into groups depending upon enamel appearance, structural and developmental defects: hypo plastic, hypo maturation, hypo calcified, and hypomaturation-hypoplastic (34).

- *Hypo plastic phase:* They are defined by the defective formation of enamel, which is composing the primary feature. The hypo plastic types can be characterized by enamel that has grooves or furrows, large missing area, or part of enamel that are very thin over the entire tooth crown. (35)Quantitative defect are seen when the enamel does not form in normal thickness either due to local or general factors. Clinically, the crown size varies from small to normal and small teeth may lack proximal contacts. The colour goes from normal to opaque white – yellow brown.(36)

- *Hypo maturation :* Qualitative defect of the enamel is seen where the enamel is not sufficiently mineralized.(15) The teeth have a normal morphologically shape at the time of eruption, but eventually chip away posteruptively, especially in the occlusal areas.

(37)Clinically, the colour of teeth here varies from creamy opaque to marked yellow/brown. The tooth surface appears soft and rough leading to sensitivity due to dentinal exposure. A common feature is find as: Open bite. The enamel thickness is normal but often chips off and abrades away easily.

- *Hypo calcified*: Qualitative defect appear when the enamel is not enough soft and mineralized. Comparing to hypo maturation type, the mineralization is markedly reduced. Clinically, the crowns of the teeth in such cases appear to be opaque white to yellow-brown, soft rough enamel surface, dental sensitivity and very poor aesthetics.(36) Due to severe hypo mineralization, there may be early loss of enamel. The thickness of enamel appears to be normal at eruption that often chips and but, tends to abrade easily post eruptive. It is find a delay eruption of teeth, an anterior open bite of skeletal origin may be seen and an accumulation of a large amount of supragingival calculus is find.(38)

5.7 Dental caries:

5.7.1 Enamel demineralisation:

Tooth decay is a disease caused by certain microorganisms in the oral cavity: cariogenic bacteria in dental plaque are the infectious agents of this disease.(39) This dental plaque is organized on the surface of the teeth from conglomerates formed of food debris, desquamated cells and certain constituents of saliva on which bacteria act.(20) The oral environment is a complex environment in which a very large number of microorganisms coexist.(40) It is a multifactorial process that involves the simultaneous relation between diet, plaque, time and the host; with the latter including a plenty of genetically related factors from saliva quantity and quality to enamel composition and structure(2).

Streptococcus mutants known as plaque bacteria have a function, which is to metabolise dietary carbohydrates within plaque to produce organic acids such as lactic, propionic and acetic acids that causes the pH reduction(41). If pH goes down below a critical value determined by the calcium and phosphate concentrations in solution, this solution will become under saturated with it will be demineralised.(42) The critical pH value is accepted when 5.5 is reached but due to substantial individual variations such as the composition of the solution surrounding enamel, this value can vary from person to person. (15)

5.7.2 Enamel remineralisation:

Early stopping or reversing the formation of caried lesions should be the main goal to prevent the risk of demineralisation and in fact the need for any invasive interventions. During enamel demineralization there is a mineral lost that can be restored by increasing the pH of the oral environment(43). Salivary buffering induces and causes pH to rise till the point when any carious destruction of the underlying tissue ceases (remineralisation). Saliva is rich in Ca2+ and PO4 3- ions, which are deposited, in the carious lesion to repair the damages.(42) Remineralisation of enamel occurs by precipitation, growth of partially dissolved crystal or by the formation of new crystals. Non-cavitated enamel lesions keeps most of their original crystalline framework of the enamel rods and the etched crystallites serve as nucleating agents for remineralisation.(15) It is a natural repair process for non-cavitated lesions. Everything relies on calcium and phosphate ions and in addition: fluoride, to re-create a new surface on the existent crystal in the subsurface. The remineralized crystals are less acid soluble than the original ones.(44). Around normal conditions pH goes to 7, saliva is supersaturated with calcium and phosphate ions, making slow caries

progression.(45)The lower is the pH, higher are the calcium and phosphate concentrations required to reach saturation with respect to hydroxyapatite.(46) This is called the “critical pH”, the point where equilibrium exists. There is no mineral dissolution and no mineral precipitation. (44)

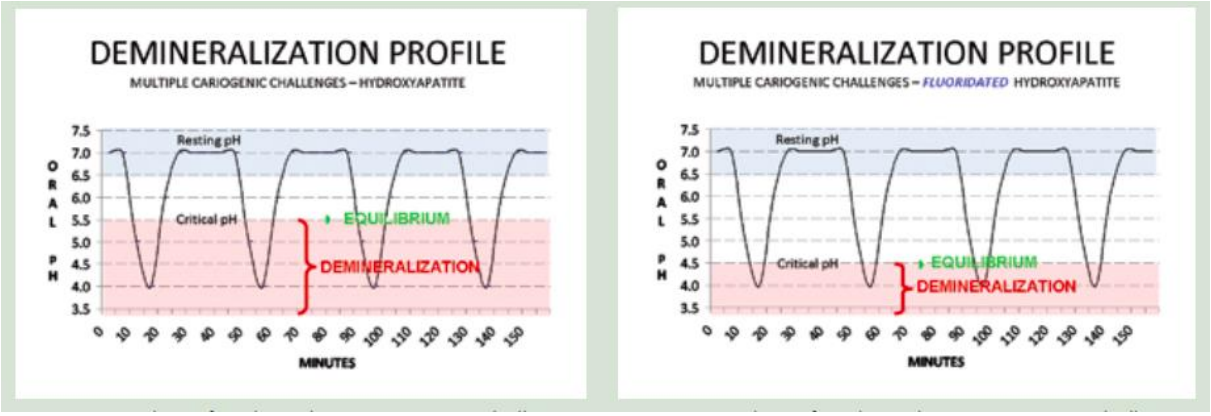


Figure 11.1 Image showing: Cycling of oral pH during cariogenic challenges in naturally occurring hydroxyapatite.(44) LEFT PICTURE.

Figure 11.2 Image showing: Cycling of oral pH during cariogenic challenges in fluoridated hydroxyapatite.(44) RIGHT PICTURE.

6. Conclusion:

The past decades of extensive research have provided the current understanding of dental enamel properties. Materials Science offers a relevant approach for the natural mineralized biological tissues and studies of enamel, technical improvements of the detection systems and recent increases in resolution allow fine descriptions of the biological phenomenon. Dental enamel is a model material for applying a physicochemical approach. Pathologies or the environment can induce destruction, degradation or enamel malformations. Unlike most other mineralized biological tissues, dental enamel is unable to regenerate naturally.

Understanding the mechanisms of enamel degradation presents a scientific and economic interest.

The interface between physics, chemistry and oral science has been very active for several decades, with a significant revival in recent years due to access to very sensitive techniques in materials science.

The help of many scientific articles allowed a better acquisition and understanding of what dental enamel and its universe really are in all chemical, biological, biochemical or genetic fields. As a result, we were able to relate these 4 fields in order to have a better enamel description.

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TABLE OF FIGURES

8. Annexes:

Microscopy

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Crystallographic structure of human tooth enamel by electron microscopy and x-ray diffraction: hexagonal or monoclinic?

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Key words. Electron diffraction, human tooth enamel, hydroxyapatite, transmission electron microscopy, X-ray analysis.

Summary

Recently reports on the major stability of the monoclinic phase of hydroxyapatite compared with the hexagonal phase have established it as the most observable structure of hydroxyapatite in natural materials, such as hard tissues. In this work, the structural and crystallographic analysis of the inorganic component of sound human tooth enamel was done by transmission electron microscopy, electron diffraction and X-ray diffraction techniques. The results indicated that its unit cell is hexagonal not monoclinic.

Introduction

Hydroxyapatite (HAP) is of notably importance because it is the major constituent of mineralized tissues in mammalian bones and teeth. In human tooth enamel it comprises 96% by volume whereas the other 4% is organic material (Le Geros, 1991). Water content varies from 1% to 6% per weight (Muster, 1992).

HAP is most frequently encountered as hexagonal (the hexagonal HAP phase hereafter) with space group symmetry $P6_3/m$ (No. 176) and lattice parameters of $a = 0.943$ nm, $c = 0.688$ nm and $\gamma = 120^\circ$ (Kay *et al.*, 1964; Sudarsanan & Young, 1969; Hughes *et al.*, 1989). Its structure consists of mirror planes at $z = ¼$ and ¾ and an array of PO_4 tetrahedra held together by Ca^{2+} ions interspersed among them. The Ca ions occur in two different sites: one in accurately aligned columns (Ca^{2+} (I)) and others in equilateral triangles (Ca^{2+} (II)). The OH^- ions occupy columns on the screw axes.

HAP also exists in monoclinic unit cell (the monoclinic HAP phase hereafter) and the reports indicate it as more ordered and thermodynamically more stable than the hexagonal HAP phase (Elliot *et al.*, 1973; Treboux *et al.*, 2000; De Leeuw, 2002; Haverty *et al.*, 2005). In addition, Takahashi *et al.* (2001) have reported the phase transition between the monoclinic and hexagonal HAP phases as reversible.

Monoclinic HAP phase has the $P2_1/b$ (No. 14) symmetry space group and lattice parameters of $a = 0.942$ nm, $b = 1.885$ nm $= 2a$, $c = 0.688$ nm and $\gamma = 120^\circ$; i.e. the monoclinic HAP unit cell parameters are similar to those of the hexagonal phase except by doubling of one of the hexagonal axes and the absence of the mirror planes: rather there are *b*-glide planes (Ikoma *et al.*, 1999). Other difference is the OH ion orientations: in the hexagonal phase they are similarly arranged in all the columns pointing in opposite directions because the mirror planes whereas in the monoclinic phase all the OH ions are pointed in the same direction (say, upper direction) in some columns but the direction is reversed (say, lower direction) in the next column (Ikoma *et al.*, 1999).

Stoichiometrically speaking, HAP in human tooth enamel does not correspond completely to the chemical formula $Ca_{10}(PO_4)_6(OH)_2$ because many elements such as Mg, Na, C and Cl are also included in its unit cell (Le Geros, 1991; Muster, 1992; Gutierrez-Salazar & Reyes-Gasga, 2003). Instead it is considered as carbonated apatite because the major inorganic impurity is the carbonate ions, which are located at the PO_4 tetrahedral sites (type II carbonate substitution) or at the OH^- sites (type I substitution) (Feki *et al.*, 1999). The carbon to oxygen ratio is close to unity, indicating that the signal for carbon and oxygen must present different sources, such as the CO_3^{2-} concentration. The content of carbonate in enamel has been set in 3.5 wt.% (Le Geros, 1991). The Ca/P ratio is sometimes close than in HAP (where it is of 1.67).

The presence of Na, Mg, Cl and C has been explained from the well-known substitutions in HAP: Ca^{2+} ($r_{Ca2+} = 99$ pm) by sodium (Na^+) ($r_{Na^+} = 102$ pm) ions; PO_4^{3-} ($r_{PO4^{3-}} = 115$ pm) by carbonates (CO_3^{2-}) ($r_{CO3^{2-}} = 178$ pm) and magnesium

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Quantitative Measurements of the Demineralisation Rates and Mineral Masses of Deciduous and Permanent Enamel

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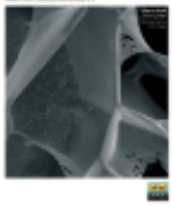

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Calcium orthophosphates

Occurrence, properties, biomineralization, pathological calcification and biomimetic applications

Sergey V. Dorozhkin

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The hidden structure of human enamel

Elia Beniash[1,2,3,4,9], Cayla A. Stifler[5,9], Chang-Yu Sun[5], Gang Seob Jung[6,7], Zhao Qin[6,7], Markus J. Buehler[6,7] & Pupa U.P.A. Gilbert[5,8]

Enamel is the hardest and most resilient tissue in the human body. Enamel includes morphologically aligned, parallel, ~50 nm wide, microns-long nanocrystals, bundled either into 5-µm-wide rods or their space-filling interrod. The orientation of enamel crystals, however, is poorly understood. Here we show that the crystalline c-axes are homogeneously oriented in interrod crystals across most of the enamel layer thickness. Within each rod crystals are not co-oriented with one another or with the long axis of the rod, as previously assumed: the c-axes of adjacent nanocrystals are most frequently mis-oriented by 1°–30°, and this orientation within each rod gradually changes, with an overall angle spread that is never zero, but varies between 30°–90° within one rod. Molecular dynamics simulations demonstrate that the observed mis-orientations of adjacent crystals induce crack deflection. This toughening mechanism contributes to the unique resilience of enamel, which lasts a lifetime under extreme physical and chemical challenges.

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ARTÍCULO ORIGINAL

Simplified chemical method of demineralization in human dental enamel

Método químico simplificado de desmineralización de esmalte dental humano

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ABSTRACT

Introduction: Abridged experimental methods are required to simulate early demineralizing lesions in a controlled and reproducible way. Objective: Perform an in vitro evaluation of a simple method of incipient enamel demineralization. **Methods**: Randomized experimental study with a double factorial replication design. Twelve third molars from healthy human subjects were selected for demineralization in a racemic lactic acid solution. Samples were then distributed randomly: Group 1 (G1) (n= 6) lactic acid at pH 2.4 and Group 2 (G2) (n= 6) lactic acid at pH 5.4. Each group was then subdivided (n= 2) to evaluate the effect of the solutions at three exposure times (7, 15 and 30 days) at 37°C. The evaluation used stereomicroscopes, a digital x-rays apparatus with software for the digital analysis of images, and polarization microscopy. An integration of the response indices was formulated and ANOVA was performed. **Results**: Visual, radiographic and histological findings showed that G1 at time 1 through 3 displayed demineralization characterized by extensive loss (80 % to 100 %) of enamel integrity. Visually, G2 at 7 days exhibited opacity and loss of brightness (16 %), with preservation of the surface structure of the enamel. **Conclusions**: It was shown that employing lactic acid for 7 days at pH 5.4 develops a clinical, radiographic and histological injury similar to an early enamel lesion.

Keywords: dental enamel; lactic acid; tooth demineralization; in vitro techniques; dental digital radiography; polarization microscopy.

http://www.revestomatologia.sld.cu/index.php/est/article/view/1407

DENTAL ENAMEL FORMATION AND IMPLICATIONS FOR ORAL HEALTH AND DISEASE

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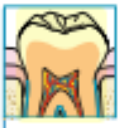

Lacruz RS, Habelitz S, Wright JT, Paine ML. Dental Enamel Formation and Implications for Oral Health and Disease. *Physiol Rev* 97: 939–993, 2017. Published May 3, 2017; doi:10.1152/physrev.00030.2016.—Dental enamel is the hardest and most mineralized tissue in extinct and extant vertebrate species and provides maximum durability that allows teeth to function as weapons and/or tools as well as for food processing. Enamel development and mineralization is an intricate process tightly regulated by cells of the enamel organ called ameloblasts. These heavily polarized cells form a monolayer around the developing enamel tissue and move as a single forming front in specified directions as they lay down a proteinaceous matrix that serves as a template for crystal growth. Ameloblasts maintain intercellular connections creating a semi-permeable barrier that at one end (basal/proximal) receives nutrients and ions from blood vessels, and at the opposite end (secretory/apical/distal) forms extracellular crystals within specified pH conditions. In this unique environment, ameloblasts orchestrate crystal growth via multiple cellular activities including modulating the transport of minerals and ions, pH regulation, proteolysis, and endocytosis. In many vertebrates, the bulk of the enamel tissue volume is first formed and subsequently mineralized by these same cells as they retransform their morphology and function. Cell death by apoptosis and regression are the fates of many ameloblasts following enamel maturation, and what cells remain of the enamel organ are shed during tooth eruption, or are incorporated into the tooth's epithelial attachment to the oral gingiva. In this review, we examine key aspects of dental enamel formation, from its developmental genesis to the ever-increasing wealth of data on the mechanisms mediating ionic transport, as well as the clinical outcomes resulting from abnormal ameloblast function.

I. INTRODUCTION

Dental enamel is the hardest substance in the human body and serves as the wear-resistant outer layer of the dental crown. It forms an insulating barrier that protects the tooth from physical, thermal, and chemical forces that would otherwise be injurious to the vital tissue in the underlying dental pulp. Because the optical properties of enamel are also derived from its structure and composition (205), developmental defects or environmental influences affecting enamel structure are typically visualized as changes in its opacity and/or color. The impact of developmental insults on enamel is critical because, unlike bone, once mineralized, enamel tissue is acellular and hence does not remodel.

In mammals, dental enamel is the only epithelial-derived tissue that mineralizes in nonpathological situations (bone and dentin, the other principal mineralized tissues, are derived from mesenchymal cells). Enamel forms within an organic matrix composed of a unique grouping of extracellular matrix proteins (EMPs) that show little homology to proteins found in other tissues. The enamel organ is formed by a mixed population of cells. Among these are ameloblasts, which are primarily responsible for enamel formation and mineralization, and form a monolayer that is in direct contact with the forming enamel surface.

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Damage modeling of small-scale experiments on dental enamel with hierarchical microstructure

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ABSTRACT

Dental enamel is a highly anisotropic and heterogeneous material, which exhibits an optimal reliability with respect to the various loads occurring over years. In this work, enamel's microstructure of parallel aligned rods of mineral fibers is modeled and mechanical properties are evaluated in terms of strength and toughness with the help of a multiscale modeling method. The established model is validated by comparing it with the stress–strain curves identified by microcantilever beam experiments extracted from these rods. Moreover, in order to gain further insight in the damage-tolerant behavior of enamel, the size of crystallites below which the structure becomes insensitive to flaws is studied by a microstructural finite element model. The assumption regarding the fiber strength is verified by a numerical study leading to accordance of fiber size and flaw tolerance size, and the debonding strength is estimated by optimizing the failure behavior of the microstructure on the hierarchical level above the individual fibers. Based on these well-grounded properties, the material behavior is predicted well by homogenization of a representative unit cell including damage, taking imperfections (like microcracks in the present case) into account.

1. Introduction

Nature has showcased the possibility of combining brittle minerals and organic proteins into composites with remarkably increased fracture resistance. Taking dental enamel as an example, the content of hydroxyapatite (HAp) is up to 96 wt.%, with the remaining portion composed of protein and water [1]. However, HAp has been limited to non-load-bearing biomedical/clinical applications because of its poor fracture resistance [2]. The reason for the significant increase toughness of biological HAp-based composites remains unresolved [3]. The general aim of the systematic characterization and investigation of existing hierarchical natural materials is to promote new ways to synthesize composite materials with equally remarkable mechanical properties.

Gao et al. [4] suggested that the impressive behavior of mineralized biological materials is due to nanometer confinement of mineral crystallites based on the theory that mineral crystallites become flaw-tolerant at the nanometer length scale. This concept has been confirmed by experimental work [5,6] which demonstrates that simultaneous improvement of hardness and toughness can be attained purely by decreasing the grain size of HAp from submicrometers to nanometers. Moreover, nanosized mineral crystallites also enable enamel having the largest hardness, as indicated, for example, by Refs. [7–9].

Enamel is usually characterized by experiments as a three-level hierarchical structure, which spans from the nanoscaled to the macroscaled level [10]; however, the hierarchical terminology was originally introduced by Koenigswald and Clemens [11], who identified up to seven hierarchical levels. The considerable amount of work published about enamel has focused on characterizing the mechanical properties either at the macroscale (millimeter) or at the nanometer scale, without taking into consideration the various hierarchical levels in the sample. That causes a large discrepancy in terms of measured hardness, elastic modulus and fracture toughness, which makes elucidation of its true structure–property relationship even more challenging [12–15]. More recently, there is an emerging interest in the role of hierarchical design by identifying the enamel's mechanical properties at each hierarchical level [7,16,17]. These works clearly reveal that nature enables enamel to possess a damage-tolerant behavior by increasing the number of hierarchy levels.

The properties of enamel depend on its position within the tooth and geometry of the sample. Consequently, there is a large variation with respect to the mechanical properties reported in

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Review Article

Dental Enamel Development: Proteinases and Their Enamel Matrix Substrates

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This review focuses on recent discoveries and delves in detail about what is known about each of the proteins (amelogenin, ameloblastin, and enamelin) and proteinases (matrix metalloproteinase-20 and kallikrein-related peptidase-4) that are secreted into the enamel matrix. After an overview of enamel development, this review focuses on these enamel proteins by describing their nomenclature, tissue expression, functions, proteinase activation, and proteinase substrate specificity. These proteins and their respective null mice and human mutations are also evaluated to shed light on the mechanisms that cause nonsyndromic enamel malformations termed *amelogenesis imperfecta*. Pertinent controversies are addressed. For example, do any of these proteins have a critical function in addition to their role in enamel development? Does amelogenin initiate crystallite growth, does it inhibit crystallite growth in width and thickness, or does it do neither? Detailed examination of the null mouse literature provides unmistakable clues and/or answers to these questions, and this data is thoroughly analyzed. Striking conclusions from this analysis reveal that widely held paradigms of enamel formation are inadequate. The final section of this review weaves the recent data into a plausible new mechanism by which these enamel matrix proteins support and promote enamel development.

1. Introduction

Tooth development is a highly orchestrated process that begins with the defined placement of individual teeth of specific shapes and sizes within the jaw. Precise signaling pathways to and from epithelial and mesenchymal cells are required for each tooth to initiate and continue along its developmental path [1, 2]. The complexity of these pathways is reflected by their high rate of incompletion. Deficiency of third molars, second premolars, and lateral incisors is common. The reported incidence of selective agenesis varies from 1.6% to 9.6% for all but third molars. Agenesis of third molars occurs in approximately 20% of the World's population [3]. Therefore, the study of tooth development has taught us how genes and tissues interact to form complex dental structures that each occupies a prespecified place within the jaw and has taught us about what can go wrong with the intricate developmental signaling pathways.

Teeth are composed of three different mineralized tissues: cementum, dentin, and enamel. Cementum is found along the tooth root and primarily serves to hold the tooth in place by binding collagen fibers (Sharpey's fibers) that are continuous with the principal fibers of the periodontal ligament. These fibers are orientated more or less perpendicularly to the cementum surface and play a major role in tooth anchorage [4]. Dentin is a bone-like matrix that forms the bulk of the tooth. It is characterized by closely packed dentinal tubules and is slightly harder than bone but softer than enamel. Dentin has an elastic quality that provides flexibility that prevents fracture of the overlying brittle enamel. Dentin and enamel are firmly bound at the dentin-enamel junction (DEJ) [4]. The enamel layer covers the crown of the tooth and is unique because it is the only epithelial derived calcified tissue in vertebrates, and it is the hardest substance in the body. Its hardness is between that of iron and carbon steel but has a higher elasticity [5]. Enamel hardness is a function of its high mineral content. Unlike bone and dentin (20–30% organic material by weight), fully formed enamel contains very little protein (less than 1% organic material) [6, 7]. Therefore, within the body, teeth are the most resistant to

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Account/Revue

Mineral studies in enamel, an exemplary model system at the interface between physics, chemistry and medical sciences

L'interface entre la physique, la chimie et l'odontologie au cours des dix dernières années : la contribution de l'émail

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ABSTRACT

Enamel is an exemplary material for physicochemical analyses of biological mineral. Hereditary and environmental enamel defects as well as secondary decay processes induce degradation and destruction of enamel matter. This exceptional mineralized tissue is unable to regenerate due to the loss of the cell forming enamel: the ameloblasts. Deciphering mechanisms of enamel degradation represent a scientific challenge of economic interest. The interface between physics, chemistry, and biomedical science has been initiated for a long time. An updated review of a classical and routinely available set of different techniques is proposed to illustrate the interface between oral sciences and physico-chemistry. Research in this field has greatly evolved over the past decade thanks to various extremely sensitive techniques in Materials Science available for translational research in biomedicine.

Mots clés:
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Diffraction des rayons X
Microscopie électronique
Dent

RÉSUMÉ

L'émail dentaire est un matériau modèle pour appliquer une approche physicochimique. Des pathologies ou l'environnement peuvent induire une destruction, une dégradation ou des malformations amélaires. Contrairement à la plupart des autres tissus biologiques minéralisés, l'émail est incapable de se régénérer naturellement. Comprendre les mécanismes de dégradation de l'émail présente un intérêt scientifique et économique. Cette revue se propose de donner un aperçu bibliographique des travaux des dix dernières années. Les études de l'émail par des techniques physiques ou chimiques classiques et disponibles ont été présentées et commentées à la lumière d'exemples récents. L'interface entre la physique, la chimie et la science orale est très active depuis plusieurs décennies, avec un important regain au cours de ces dernières années en raison de l'accès à des techniques très sensibles de la science des matériaux.

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Etiology and Considerations of Developmental Enamel Defects in Children: A Narrative Review

Article in Journal of Pediatrics Review · July 2019

DOI: 10.32388/jpr.1.3.141

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Tooth Enamel

tooth enamel is the hardest biological substance in the human body, and posterior teeth are well protected by soft tissues (the tongue, facial musculature, and adipose tissue).

From: Forensic Odontology, 2018

Related terms:

Dental Caries, Dentin, Hydroxylapatite, Lesion, Resin, Protein, Salicylic Acid, Fluoride

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Fundamentals of Human Bone and Dental Biology

Niels Lynnerup, Haagen D. Klaus, in Ortner's Identification of Pathological Conditions in Human Skeletal Remains (Third Edition), 2019

Enamel

Enamel is the hardest material produced by biological processes. It is derived from the epithelium and forms the anatomical crown of a tooth. Composed of approximately 96% inorganic apatite crystals and 4% organic material and water, this highly mineralized, acellular, and avascular tissue has been shaped by natural selection for its abrasion-resistant properties. To these ends, enamel apatite crystals are packed together as parallel alternating crystallite enamel rods and inter-rod enamel (Nanci, 2017). Enamel thickness varies on the dental crown, being thickest on the buccal surfaces (about 2.5 mm) and thinner toward the cervix. Enamel is translucent and varies in color from yellowish to grayish white. Ameloblasts, or enamel-forming cells, eventually disappear as the development completes. Accordingly, enamel cannot be repaired or remodeled. An enamel defect or chipping/spalling damage is permanent. Therefore, diseases that have an impact on enamel formation may leave permanent "scars" in the enamel structure.

Hydroxyapatite

Hydroxyapatite (HAp) is a calcium phosphate–derived mineral presenting morphology and composition similar to those of the human hard tissues [59].

From: Nanocarriers for Drug Delivery, 2019

Related terms:

Phosphate, Inorganic Ions, Apatite, Biomaterial, Enzyme, Protein, Calcium Phosphate

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Alloplastic Implantation

Stephen Daane MD, in Plastic Surgery Secrets Plus (Second Edition), 2010

9 How is HA used in plastic surgery?

HA is available in block form (porous or solid) and as granules. It is used most commonly to augment the contour of the facial skeleton or as a bone graft substitute in orthognathic surgery. Contouring of HA blocks is performed with dental burs. Lag screw fixation is suggested when HA blocks are placed in an onlay manner because osteointegration will not occur if the blocks are mobile.

Experimentally, porous HA blocks and HA granules are rapidly invaded by fibrovascular tissue. Histologic evidence of direct osseous union between implant and bone is seen within 2 to 3 months. HA is "osteoconductive" in that it provides a matrix for deposition of new bone from adjacent living bone. HA is not "osteogenic" because it will not induce bone formation when placed in ectopic sites such as muscle or fat. Long-term radiographic follow-up shows a lack of resorption of HA implants.

HA blocks are brittle but gain rapidly in strength as the implant pores are invaded by fibrovascular tissue. The ultimate compressive strength exceeds the masticatory forces of the jaws. Infection is likely to occur when there is a deficiency of soft tissue coverage.

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REVIEW

Review of research on the mechanical properties of the human tooth

Ya-Rong Zhang*, Wen Du*, Xue-Dong Zhou and Hai-Yang Yu

'Bronze teeth' reflect the mechanical properties of natural teeth to a certain extent. Their mechanical properties resemble those of a tough metal, and the gradient of these properties lies in the direction from outside to inside. These attributes confer human teeth with effective mastication ability. Understanding the various mechanical properties of human teeth and dental materials is the basis for the development of restorative materials. In this study, the elastic properties, dynamic mechanical properties (visco-elasticity) and fracture mechanical properties of enamel and dentin were reviewed to provide a more thorough understanding of the mechanical properties of human teeth.
International Journal of Oral Science (2014) **6**, 61–69; doi:10.1038/ijos.2014.21; published 18 April 2014

Keywords: dentin; enamel; fatigue crack growth; fracture toughness; mechanical property

INTRODUCTION

'Bronze teeth' reflect the mechanical properties of natural teeth to a certain extent. Their mechanical properties resemble those of a tough metal, and they vary from the outside to inside of teeth. These attributes confer human teeth with effective mastication ability.[1] The unique mechanical properties of natural teeth enable them to perform the functions of incision, laceration, and grinding of food during mastication.[2] To date, a material that can completely take the place of human teeth with regard to biological and mechanical properties has not yet been found. Human teeth have a more complicated structure, better mechanical properties and better biocompatibility than all dental restorative materials, including synthetic resin materials, ceramic materials and dental alloys. Understanding the various mechanical properties of natural teeth is the basis of dental restoration materials research and can provide a reference for evaluating the mechanical properties of new dental materials.[3] The elastic properties, dynamic mechanical properties (visco-elasticity) and fracture mechanical properties of human enamel and dentin are reviewed in this article, thus providing a more comprehensive understanding of the mechanical properties of human teeth.

The mechanical properties of human teeth are determined by their structure and composition. The structure of natural teeth consists of enamel, dentin, cementum and dental pulp, the first three of which constitute the hard tissue of the human tooth and are characterized by unique mechanical properties. The composition and structure of teeth are presented in Table 1.

The enamel rod, a 'keyhole-like' structure with a diameter of approximately 5 μm, is perpendicular to the dentinal–enamel junction[4] and is mainly composed of hexagonal prism hydroxyapatite crystals with a 68-nm length, 26-nm diameter and 2-nm protein thickness.[5] The hydroxyapatite crystals at the centre are parallel to the long axis of the rod itself; however, the crystals at the margin of the rod form a 45° angle to the axis.[6] Two crystals in the enamel meet at sharp angles and form a 'fish-scale' or 'keyhole-like' appearance referred to as the rod sheath. The rod sheath consists of more protein than other areas of the enamel and is hypomineralized compared with the remainder of the highly mineralized enamel. Thus, the enamel has an anisotropic mechanical property.

Dentin is the tissue that lies beneath the enamel and surrounds the pulp chamber and root canals. The dentin microstructure consists of dentinal tubules that radiate outward through the dentin from the pulp to the exterior cementum or enamel border. Peritubular dentin and intertubular dentin contain rich collagen fibres. The dentinal tubules are wrapped with peritubular dentin. The size, quantity and wall thickness of dentinal tubules vary from outside to inside.[7]

Cementum has a structure similar to that of bone tissue but has a lower hardness than dentin. The main inorganic components of cementum exist in the form of apatites that primarily contain calcium ion, and its organic components consist of collagen and non-collagen proteins. Cementum can be divided into acellular cementum and cellular cementum. The acellular cementum is formed by the cementum lamina, which is tightly attached to the surface of the

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Crystallographic and Microstructural Studies of Dental Enamel using Synchrotron X-ray Diffraction and Complementary Techniques

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(BSc Hons)

Supervised by Dr Maisoon Al-Jawad and Dr Graham Davis

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2014

Dental Physical Sciences Unit, Centre for Oral Growth and Development, Institute of Dentistry, Barts and The London School of Medicine and Dentistry, Queen Mary University of London

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THESE

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OPTIMISATION DU COLLAGE A L'EMAIL ET A LA DENTINE

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Enamel remineralization: controlling the caries disease or treating early caries lesions?§

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Abstract: The emphasis currently given to new technologies for enamel remineralization suggests that the changes in the understanding of the dental caries disease, which occurred in the last century, were either not yet adopted or were forgotten. Just like in the past, when the disease was "treated" by restoring cavities, there is presently a misunderstanding on the concept of incipient lesion remineralization. The aim of this paper was to review some concepts about caries, the natural phenomenon of enamel remineralization and the effect of fluoride (F) on it, and also to discuss the clinical relevance of remineralizing products recently launched in the marketplace aiming to "treat early caries lesions".

Descriptors: Dental caries; Dental enamel; Tooth remineralization; Fluorides.

§Paper presented at the "Oral Health Self-Care Products: Realities and Myths" international symposium, sponsored by the Brazilian Association for Oral Health Promotion (ABOPREV), September 25-27, 2008, São Paulo, SP, Brazil.

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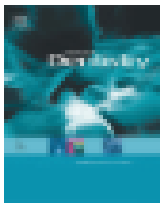

Enamel mineral loss

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KEYWORDS

Enamel
Demineralisation
Abrasion
Erosion
Attrition
Caries

ABSTRACT

Objectives: To summarise the chemical, biological and host factors that impact enamel mineral loss, to highlight approaches to contemporary management of clinical conditions involving mineral loss and summarise emerging trends and challenges in this area.

Data sources: "Medline" and "Scopus" databases were searched electronically with the principal key words tooth, enamel, "mineral", caries and erosion. Language was restricted to English and original studies and reviews were included. Conference papers and abstracts were excluded.

Conclusions: Enamel mineral loss leads to the degradation of the surface and subsurface structures of teeth. This can impact their shape, function, sensitivity and aesthetic qualities. Dental caries is a multifactorial disease caused by the simultaneous interplay of dietary sugars, dental plaque, the host and time. There is a steady decline in dental caries in developed countries and the clinical management of caries is moving towards a less invasive intervention, with risk assessment, prevention, control, restoration and recall. Tooth wear can be caused by erosion, abrasion and attrition. Dental erosion can be the result of acid from intrinsic sources, such as gastric acids, or extrinsic sources, in particular from the diet and consumption of acidic foods and drinks. Its prevalence is increasing and it increases with age. Clinical management requires diagnosis and risk assessment to understand the underlying aetiology, so that optimal preventative measures can be implemented. Overall, prevention of enamel mineral loss from caries and tooth wear should form the basis of lifelong dental management. Evidence based oral hygiene and dietary advice is imperative, alongside preventive therapy, to have a healthy lifestyle, whilst retaining hard tooth tissue.

1. Introduction

Human permanent teeth are designed to last a lifetime, having an outer coating of the hardest tissue in the human body and being surrounded by an oral environment (e.g. saliva, pellicle) that aids the stability and protection of the teeth. This combination generally helps to preserve their natural function throughout life. However, despite their inherent strength and the protective qualities of the oral environment, a variety of other factors can act to cause the loss of tooth enamel minerals and dental tissue. These factors include acids generated by bacteria in plaque following metabolism of fermentable carbohydrates derived from the diet and tooth wear processes such as erosion due to acidic diets and/or physical insults such as abrasion or attrition. The result of enamel mineral loss can be the degradation of the surface and the subsurface enamel which can lead to changes in tooth hardness, shape, function, aesthetic qualities, increased sensitivity and even ultimately to complete tooth loss. In the current era of improved dental health awareness and care,

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Biomineralization and Biomimicry of Tooth Enamel

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Review Article

Dental Enamel Development: Proteinases and Their Enamel Matrix Substrates

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This review focuses on recent discoveries and delves in detail about what is known about each of the proteins (amelogenin, ameloblastin, and enamelin) and proteinases (matrix metalloproteinase-20 and kallikrein-related peptidase-4) that are secreted into the enamel matrix. After an overview of enamel development, this review focuses on these enamel proteins by describing their nomenclature, tissue expression, functions, proteinase activation, and proteinase substrate specificity. These proteins and their respective null mice and human mutations are also evaluated to shed light on the mechanisms that cause nonsyndromic enamel malformations termed *amelogenesis imperfecta*. Pertinent controversies are addressed. For example, do any of these proteins have a critical function in addition to their role in enamel development? Does amelogenin initiate crystallite growth, does it inhibit crystallite growth in width and thickness, or does it do neither? Detailed examination of the null mouse literature provides unmistakable clues and/or answers to these questions, and this data is thoroughly analyzed. Striking conclusions from this analysis reveal that widely held paradigms of enamel formation are inadequate. The final section of this review weaves the recent data into a plausible new mechanism by which these enamel matrix proteins support and promote enamel development.

1. Introduction

Tooth development is a highly orchestrated process that begins with the defined placement of individual teeth of specific shapes and sizes within the jaw. Precise signaling pathways to and from epithelial and mesenchymal cells are required for each tooth to initiate and continue along its developmental path [1, 2]. The complexity of these pathways is reflected by their high rate of incompletion. Deficiency of third molars, second premolars, and lateral incisors is common. The reported incidence of selective agenesis varies from 1.6% to 9.6% for all but third molars. Agenesis of third molars occurs in approximately 20% of the World's population [3]. Therefore, the study of tooth development has taught us how genes and tissues interact to form complex dental structures that each occupies a prespecified place within the jaw and has taught us about what can go wrong with the intricate developmental signaling pathways.

Teeth are composed of three different mineralized tissues: cementum, dentin, and enamel. Cementum is found along the tooth root and primarily serves to hold the tooth in place by binding collagen fibers (Sharpey's fibers) that are continuous with the principal fibers of the periodontal ligament. These fibers are orientated more or less perpendicularly to the cementum surface and play a major role in tooth anchorage [4]. Dentin is a bone-like matrix that forms the bulk of the tooth. It is characterized by closely packed dentinal tubules and is slightly harder than bone but softer than enamel. Dentin has an elastic quality that provides flexibility that prevents fracture of the overlying brittle enamel. Dentin and enamel are firmly bound at the dentin-enamel junction (DEJ) [4]. The enamel layer covers the crown of the tooth and is unique because it is the only epithelial derived calcified tissue in vertebrates, and it is the hardest substance in the body. Its hardness is between that of iron and carbon steel but has a higher elasticity [5]. Enamel hardness is a function of its high mineral content. Unlike bone and dentin (20–30% organic material by weight), fully formed enamel contains very little protein (less than 1% organic material) [6, 7]. Therefore, within the body, teeth are the most resistant to

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Bandas de Hunter-Schreger: Propuesta Terminológica

Hunter-Schreger Bands: Terminological Propose

Ignacio Rua[1,2] & Nikol Ponce[2,3]

RUA, I. & PONCE, N. Bandas de Hunter-Schreger: Propuesta terminológica. *Int. J. Morphol., 37(4)*:1210-1212, 2019.

RESUMEN: Las Bandas de Hunter–Schreger (BHS), son bandas claras y oscuras, que se aprecian en el esmalte debido a la distinta curvatura de los prismas del esmalte, resultan ser ampliamente mencionadas en estudios, tanto odontológicos como antropológicos, mas no se ven reflejadas en *Terminologia Histologica*. El objetivo del presente trabajo fue realizar un análisis del término BHS, con el fin de proponerlo como nuevo término histológico, y así poder ser incluido en *Terminologia Histologica* por la Federative International Programme for Anatomical Terminology (FIPAT). Luego del análisis en textos de estudio y publicaciones científicas, proponemos en reemplazo del término BHS, por dos términos: *diazona prismatica* (*diá* del griego διά 'a través de' y del griego *zonʼei* ζωνη 'faja', 'zona de la tierra') y *parazona prismatica* (*pará* παρά gr. 'a lo largo de' y del griego *zonʼei* ζωνη 'faja', 'zona de la tierra'), definiendo así términos más descriptivos y que no utilizan epónimos, tal como lo establece la Terminología Internacional. Proponer nuevos términos que estén más acorde con los señalado por la International Federation of Associations of Anatomists (IFAA) y la propia terminología, presenta grandes desafíos; un término no sólo es una palabra que hace referencia a una estructura morfológica, sino que también es una unidad del lenguaje, que une a la comunidad morfológica en un solo lenguaje. Por lo cual proponemos que el término sea incluido por la FIPAT en próximas discusiones.

PALABRAS CLAVE: Bandas de Hunter-Schreger; Esmalte; *Terminología Histológica*.

INTRODUCTION

La compleja microestructura interna del esmalte, refleja la naturaleza del mecanismo detrás de su formación y las exigencias biomecánicas a las que se encuentra expuesto (Rensberger, 1997). Es así como durante la secreción de esmalte por parte de los ameloblastos, son formadas una serie de estructuras, dentro de ellas los prismas del esmalte; bastones alargados de trayecto ondulado, formados por cristales de hidroxiapatita, que se extienden desde la unión amelodentinaria hasta la superficie (Osborne, 1973; Lynch *et al*., 2010) (Fig.1). Al hacer incidir luz sobre la superficie seccionada longitudinalmente del esmalte, son apreciadas bandas claras-oscuras, observadas principalmente por el trayecto irregular de los prismas del esmalte. Dichas bandas claras y oscuras; son las llamadas Bandas de Hunter–Schreger (BHS) (Arrieta *et al*., 2018) (Fig. 2).

Como ya ha sido analizado con anterioridad, son múltiples las estructuras de la Histología oral, que se encuentran excluidas de *Terminologia Histologica* (Rua & Navarrete, 2018). En dichos términos aún predomina el uso de epónimos y sinónimos; siendo estas denominaciones muchas veces poco descriptivas (Rua & Navarrete, 2018), aunque ampliamente utilizadas, como es el caso de BHS (Ramenzoni & Line, 2006; von Koenigswald *et al*., 2010; Lynch *et al*., 2010, 2011; Tserig, 2011).

El objetivo del presente estudio fue realizar un análisis del término BHS con el fin de modificarlo y proponer un nuevo término histológico a ser incluido en *Terminologia Histologica* por la Federative International Programme for Anatomical Terminology (FIPAT).

ANÁLISIS DE LA TERMINOLOGÍA Y DISCUSIÓN

El término BHS, describe a las bandas claro-oscuras presentes en el esmalte de un diente seccionado longitudinalmente al momento de incidir la luz en él, formadas por las secciones de los prismas, pudiendo invertirse

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Mechanical behaviour of human enamel and the relationship to its structural and compositional characteristics

by

Lihong He

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Development of Teeth

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Review

Tooth Enamel and Its Dynamic Protein Matrix

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Abstract: Tooth enamel is the outer covering of tooth crowns, the hardest material in the mammalian body, yet fracture resistant. The extremely high content of 95 wt% calcium phosphate in healthy adult teeth is achieved through mineralization of a proteinaceous matrix that changes in abundance and composition. Enamel-specific proteins and proteases are known to be critical for proper enamel formation. Recent proteomics analyses revealed many other proteins with their roles in enamel formation yet to be unraveled. Although the exact protein composition of healthy tooth enamel is still unknown, it is apparent that compromised enamel deviates in amount and composition of its organic material. Why these differences affect both the mineralization process before tooth eruption and the properties of erupted teeth will become apparent as proteomics protocols are adjusted to the variability between species, tooth size, sample size and ephemeral organic content of forming teeth. This review summarizes the current knowledge and published proteomics data of healthy and diseased tooth enamel, including advancements in forensic applications and disease models in animals. A summary and discussion of the status quo highlights how recent proteomics findings advance our understating of the complexity and temporal changes of extracellular matrix composition during tooth enamel formation.

Keywords: tooth enamel; enamel proteome; amelogenin; amelogenin-Y (AMELY); enamel peptide; molar hypomineralization; dental anthropology; dental fluorosis; serum albumin

1. Introduction

In recent years, the number of proteins implicated in tooth formation and, in particular, tooth enamel mineralization has grown considerably. This is partly due to studies on gene expression, partly based on advances in proteomic analyses of tooth enamel that have provided an expanded list of proteins and peptides. While these findings deepen our understanding, they also highlight the unique features of the mineralizing tooth enamel matrix, such as proteins specific to tooth enamel. One key difference between tooth enamel, bone and dentin is that the protein matrix changes during enamel formation dramatically in both abundance and composition, decreasing from 35 percent dry weight leaving in erupted teeth less than one percent by weight of protein as an entombed fossil record of ontogeny [1].

Tooth analyses are increasingly used in the biomedical field to obtain individual histories of health and exposure to adversities during prenatal as well as postnatal development [2,3]. This use of teeth as a biomarker leverages several unique features of tooth formation, including the known timing of tooth development in humans during discrete periods in ontogeny, an incremental process of formation, the absence of turn-over after formation and the accessibility of shed or extracted teeth [4]. However, there is growing interest in unlocking the organic record preserved in tooth enamel. This is a prerequisite to better understand the factors contributing to enamel formation but also gives access to histories of exposure to organic toxicants. Proteomic analyses have become critical to expand our

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Tooth shape formation and tooth renewal: evolving with the same signals

Jukka Jernvall* and Irma Thesleff*

Summary

Teeth are found in almost all vertebrates, and they therefore provide a general paradigm for the study of epithelial organ development and evolution. Here, we review the developmental mechanisms underlying changes in tooth complexity and tooth renewal during evolution, focusing on recent studies of fish, reptiles and mammals. Mammals differ from other living vertebrates in that they have the most complex teeth with restricted capacity for tooth renewal. As we discuss, however, limited tooth replacement in mammals has been compensated for in some taxa by the evolution of continuously growing teeth, the development of which appears to reuse the regulatory pathways of tooth replacement.

Key words: Evo-devo, Patterning, Teeth, Tooth shape, Tooth replacement

Introduction

For the past 20 years, teeth have been used extensively as models in analyses related to developmental patterning, signaling and evolution. During mouse embryogenesis, the late onset of tooth development (odontogenesis) makes the mouse dentition an accessible model system for diverse types of developmental studies. As a result, teeth constitute a developmental module that can be studied in relative isolation. The wealth of data on tooth development is rivaled by the central role of dentitions in documenting the evolutionary history of vertebrates. The relative completeness of the vertebrate fossil record is due in no small part to the hardness, and hence preservability, of teeth. Furthermore, unlike other epithelial-based organs, such as hair, scales and feathers, teeth are found throughout vertebrate groups, thus providing a general paradigm for studying the evolution and development of epithelial organs.

The basic steps of tooth morphogenesis were described well over 100 years ago and are basically similar in all vertebrates (e.g. Owen, 1845; Leche, 1895) (Fig. 1). Briefly, tooth formation is regulated by epithelial-mesenchymal interactions; the mesenchyme derives from the neural crest, whereas the epithelium may be ectodermal or endodermal (Soukup et al., 2008; Fraser et al., 2009). The establishment of the dental lamina, the area that forms teeth, precedes the initiation of individual teeth. Teeth become visible during the following stages of development, called the bud and the cap stages, in which the initial epithelial invagination and the tooth crown area, respectively, appear. The cap stage is followed by the bell stage, during which species-specific cusp patterns emerge. After the formation of the cusp pattern, the tooth grows to its final size, and mesenchymal odontoblasts and epithelial ameloblasts differentiate at the epithelial-mesenchymal interface to form dentin and enamel, respectively. These hard dental tissues, together with cementum, which is made by cementoblasts, have largely similar compositions in all vertebrates, with enamel being up to 98% hydroxyapatite.

Research during the past 20 years has uncovered the iterative use of largely the same molecular pathways throughout the various stages of tooth development (Jernvall and Thesleff, 2000; Bei, 2009; Tummers and Thesleff, 2009). Members of the transforming growth factor β (TGFβ), fibroblast growth factor (FGF), sonic hedgehog (Shh) and Wnt signaling pathways are all required repeatedly during tooth development, and the abolition of any of these pathways results in a developmental arrest of teeth, most commonly at the bud stage. These different pathways are integrated at several stages of the tooth development process and the overall regulatory network is highly conserved in evolution (Jernvall and Thesleff, 2000; Fraser et al., 2009).

Much of the past research in this field has focused on four 'life history' stages of the tooth: determination of tooth-forming regions, initiation of tooth formation, determination of tooth shape and regulation of tooth renewal. Whereas the number of tooth-forming regions and the number of teeth show an evolutionary tendency to decrease (reviewed by Davit-Béal et al., 2009), tooth shape complexity and tooth renewal increase through time (Fig. 2). Below, we focus on these increases in dental complexity and tooth renewing capacity, and review both the evolutionary patterns and developmental mechanisms underlying these changes in fish, reptiles and mammals.

Making a tooth: shape formation and shape modification

Prior to the initiation of tooth development, the dental lamina, which is also known as the odontogenic band, appears within the dental epithelium. The lamina forms as a thickening of the epithelium and restricts the tooth-forming area laterally (Fig. 1). Even though the molecular mechanisms of dental lamina formation are currently unknown, several studies have shown that sonic hedgehog (*Shh*) and pituitary homeobox 2 (*Pitx2*) are expressed in the dental lamina in several taxa (Kavanen et al., 1999; Fraser et al., 2006; Smith et al., 2009; Buchtova et al., 2008; Vonk et al., 2008). From within the lamina, individual teeth are initiated, and this process can be seen, at least in mammals, by a gradual restriction of *Shh* and *Pitx2* expression to the specific domains, referred to as placodes, that give rise to teeth.

After the initiation of tooth development, the morphology of individual teeth unfolds during the bud, cap and bell stages (Fig. 1). These developmental stages are crucial for the survival of the animal because the correct function of teeth depends almost entirely on the patterns established prior to tooth eruption. Once erupted, the tooth morphology changes only through wear or damage, and there is no remodeling of the mineralized tissue, unlike the rest of the skeleton. The lack of remodeling also implies that the evolutionary modification of tooth morphology happens during its ontogeny.

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Amelogenic transcriptome profiling in ameloblast-like cells derived from adult gingival epithelial cells

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Sun-Yi Hyun[1], Seyoung Mun[1,2], Kyung-Jung Kang[1], Jong-Chan Lim[1], Shin-Young Kim[1], Kyudong Han[1,2] & Young-Joo Jang[1]

Dental enamel is the highly mineralized tissue covering the tooth surface and is formed by ameloblasts. Ameloblasts have been known to be impossible to detect in adult tooth because they are shed by apoptosis during enamel maturation and tooth eruption. Owing to these, little was known about appropriate cell surface markers to isolate ameloblast-like cells in tissues. To overcome these problems, epithelial cells were selectively cultivated from the gingival tissues and used as a stem cell source for ameloblastic differentiation. When gingival epithelial cells were treated with a specified concentration of BMP2, BMP4, and TGFβ-1, the expression of ameloblast-specific markers was increased, and both the MAPK and Smad signaling pathways were activated. Gingival epithelial cells differentiated into ameloblast-like cells through epithelial-mesenchymal transition. By RNA-Seq analysis, we reported 20 ameloblast-specific genes associated with cell surface, cell adhesion, and extracellular matrix function. These cell surface markers might be useful for the detection and isolation of ameloblast-like cells from dental tissues.

Dentin, dental pulp, periodontal ligament, and dental enamel are developed by reciprocal interactions between dental epithelium and ectomesenchyme. Neural crest cell-derived ectomesenchyme differentiates into odontoblasts, periodontal ligament progenitors, cementoblasts, as well as various fibroblasts. On the other hand, enamel-forming ameloblasts differentiate from epithelial cells originating from oral ectoderm. In the process of enamel formation, the inner enamel epithelium differentiates into ameloblasts[1]. Ameloblastic differentiation possibly occurs after the initial dentin matrix protein secretion and deposition by odontoblasts[2,3]. The enamel matrix proteins (EMPs) are degraded by various proteinases secreted by ameloblasts and replaced by minerals during the maturation stage[4]. Hertwig's epithelial root sheath/epithelial cell rests of Malassez (HERS/ERM) have been reported to be a unique epithelial cell source[5,6]. Bone marrow stromal cells, embryonic stem cells, and skin epithelial cells are alternative sources for the construction of ameloblasts[7]. Induction mechanism of various progenitors is strictly regulated by growth factors and cytokines, such as TGFs, FGFs, Wnts, and BMPs, as well as the extracellular matrix in the epithelium and mesenchyme[8,9]. In ameloblastic differentiation, BMP2 and BMP4 are secreted by ectomesenchymal odontoblasts and play important roles in the expression of EMPs and terminal differentiation of ameloblasts[10,11]. Ameloblast differentiation is prevented by follistatin by antagonizing the inductive effect of BMP4 from the odontoblasts. The expression of follistatin is shown to be induced by activin A from the overlying mesenchymal follicle cells. Thus, a balance between BMP4 and activin A, is required for proper ameloblast differentiation[12]. In addition, knockout of a BMP receptor, Bmpr1a/ALK3, causes defective enamel formation on tooth crowns[13]. Besides BMPs, TGFβ-1 stimulates the expression and secretion of EMPs in ameloblasts. The inhibition of the TGFβ-1 signaling pathway causes tooth and enamel malformations[14,15]. The Smad signaling is known as an intracellular canonical pathway activated by TGF-β superfamily members through a heteromeric receptor complex, comprised of type I and type II receptors[16,17]. According to the activation of receptors by TGFβ-1 and BMPs, Smad2/3 and Smad1/5/8, which are known as the regulatory Smads (R-Smads) are phosphorylated, respectively, and then, a complex of phospho-R-Smads and Smad4 regulates the expression of target genes in the nucleus[18,19].

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Original Article

A Long-Term Clinical Study on Individuals with Amelogenesis Imperfecta

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Abstract

Background: The aims of this study are to present sociodemographic and familial characteristics, clinical and systemic findings, dental treatment needs, and concomitant dental anomalies in patients with amelogenesis imperfecta (AI) and to evaluate time-varying conditions in these long-term follow-up patients. **Materials and Methods:** Records of patients with AI who were examined in the Department of Pediatric Dentistry between 1999 and 2017 were reviewed. Information about sociodemographic characteristics, history of AI and consanguinity in family, systemic conditions, reasons for referral to the clinic, oral hygiene habits and gingival health, occlusion findings, and performed treatments were gathered. Dental anomalies in radiographs were also evaluated. Baseline and final situations of the patients were assessed. Statistical analyses were performed. **Results:** Of 75 patients aged 3–15 years with follow-ups up to 12 years, 34 had AI in their families and 15 were born from consanguineous marriages. Nephrocalcinosis has been observed in 5 patients. Main reasons for referral to the clinic were related to esthetic and hypersensitivity concerns. Twenty-two patients had gingivitis, and during follow-up process, gingival problems could not be completely prevented due to poor oral hygiene habits. Vertical dimension loss, open-bite, and cross-bite were seen in 16, 15, and 10 patients, respectively. Of the patients, 63% experienced restorative, 33% stainless steel crown, 17% endodontic, 8% prosthetic treatments, and 24% had retreatment needs. Concomitant dental anomalies were dens invaginatus, taurodontism, ectopic eruption, delayed eruption, hypodontia, and pulpal calcification. **Conclusion:** Early diagnosis and interventions considering the time-varying conditions with long-term follow-ups provide significant improvements in clinical maintenance of patients with AI.

Keywords: *Amelogenesis imperfecta, children, follow-up, health, prognosis*

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Introduction

Amelogenesis imperfecta (AI) is a rare condition with genetic transmission, which affects the enamel structure, quantity, and composition of primary and permanent teeth.[1] Its prevalence has been enounced to vary between 1/718 and 1/14,000 depending on the study population.[2] It has been reported that this condition has autosomal dominant, autosomal recessive, or rarely, X chromosome-linked inheritance patterns[3] and that it may also be transmitted by consanguineous marriages.[4,5] On the other hand, different researchers have reported that AI may develop when a mutation occurs in genes.[6-8]

The diagnosis of AI can be established by anamnesis followed by clinical and radiographic evaluations and genetic analyses.

It has been represented that some additional dental anomalies may develop in patients with AI.[9-11] Hypersensitivity is a common complaint in teeth due to the structure of enamel. The goals of treatment, with

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Review

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Amelogenesis imperfecta

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Abstract

Amelogenesis imperfecta (AI) represents a group of developmental conditions, genomic in origin, which affect the structure and clinical appearance of enamel of all or nearly all the teeth in a more or less equal manner, and which may be associated with morphologic or biochemical changes elsewhere in the body. The prevalence varies from 1:700 to 1:14,000, according to the populations studied. The enamel may be hypoplastic, hypomineralised or both and teeth affected may be discoloured, sensitive or prone to disintegration. AI exists in isolation or associated with other abnormalities in syndromes. It may show autosomal dominant, autosomal recessive, sex-linked and sporadic inheritance patterns. In families with an X-linked form it has been shown that the disorder may result from mutations in the amelogenin gene, AMELX. The enamelin gene, ENAM, is implicated in the pathogenesis of the dominant forms of AI. Autosomal recessive AI has been reported in families with known consanguinity. Diagnosis is based on the family history, pedigree plotting and meticulous clinical observation. Genetic diagnosis is presently only a research tool. The condition presents problems of socialisation, function and discomfort but may be managed by early rigorous intervention, both preventively and restoratively, with treatment continued throughout childhood and into adult life. In infancy, the primary dentition may be protected by the use of preformed metal crowns on posterior teeth. The longer-term care involves either crowns or, more frequently these days, adhesive, plastic restorations.

Disease name

Amelogenesis imperfecta (AI) is a term for a clinically and genetically heterogeneous group of conditions that affect the dental enamel, occasionally in conjunction with other dental, oral and extraoral tissues.

Definition and diagnosis criteria

AI represents a group of conditions, genomic in origin, which affect the structure and clinical appearance of the enamel of all or nearly all the teeth in a more or less equal manner, and which may be associated with morphologic or biochemical changes elsewhere in the body [1]. AI is a developmental condition of the dental enamel (characterised by hypoplasia and/or hypomineralisation) that shows autosomal dominant, autosomal recessive, sex-linked and sporadic inheritance patterns, as well as sporadic cases.

Signaling Networks Regulating Tooth Organogenesis and Regeneration, and the Specification of Dental Mesenchymal and Epithelial Cell Lineages

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Cold Spring Harbor Perspectives in Biology

SUMMARY

Teeth develop as ectodermal appendages from epithelial and mesenchymal tissues. Tooth organogenesis is regulated by an intricate network of cell–cell signaling during all steps of development. The dental hard tissues, dentin, enamel, and cementum, are formed by unique cell types whose differentiation is intimately linked with morphogenesis. During evolution the capacity for tooth replacement has been reduced in mammals, whereas teeth have acquired more complex shapes. Mammalian teeth contain stem cells but they may not provide a source for bioengineering of human teeth. Therefore it is likely that nondental cells will have to be reprogrammed for the purpose of clinical tooth regeneration. Obviously this will require understanding of the mechanisms of normal development. The signaling networks mediating the epithelial-mesenchymal interactions during morphogenesis are well characterized but the molecular signatures of the odontogenic tissues remain to be uncovered.

Outline

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BMC Oral Health

RESEARCH ARTICLE Open Access

Remineralization of enamel subsurface lesions using toothpaste containing tricalcium phosphate and fluoride: an in vitro μCT analysis

Hidenori Hamba[1,2*], Keiki Nakamura[1], Toru Nikaido[3], Junji Tagami[2] and Takashi Muramatsu[1]

Abstract

Background: This study aimed to compare the efficacies of experimental toothpastes containing functionalized tricalcium phosphate (fTCP) with and without fluoride for in vitro enamel remineralization under pH-cycling conditions.

Methods: To create artificial white spot lesions, 36 bovine enamel specimens were immersed in a demineralization solution for 10 days. During pH-cycling for 12 days, the specimens were divided into four groups based on the experimental toothpaste type used: (a) fTCP-free, fluoride-free (fTCP − F −); (b) fTCP-containing, fluoride-free (fTCP + F −); (c) fTCP-free, fluoride-containing (fTCP − F +); and (d) fTCP-containing, fluoride-containing (fTCP + F +). Micro-focus X-ray computed tomography (μCT) scans of all specimens were obtained before demineralization, after demineralization, and after pH-cycling. The mineral density and mineral loss (ΔZ) in the enamel subsurface lesions were measured and the percentage of remineralization (%R) was calculated from ΔZ after demineralization and pH-cycling. One-way ANOVA with Tukey's test was used for statistical analysis of the %R values. The treated enamel surface was investigated via scanning electron microscopy (SEM).

Results: The fTCP − F − group presented with the lowest amount of mineral gain after pH-cycling. In contrast, the fTCP + F + group showed the highest degree of remineralization within all lesion parts. The %R was highest in the fTCP + F + group (38.2 ± 7.8, all $P < 0.01$). SEM revealed the presence of small crystals on the enamel rods in the fTCP + F − and fTCP + F + groups.

Conclusions: The experimental toothpaste containing fTCP and fluoride increased remineralization of the artificial enamel subsurface lesions during pH-cycling. Furthermore, fTCP and fluoride appear to act independently on the remineralization of enamel subsurface lesions, although they coexisted in one toothpaste type.

Trial registration: This is not a human subject research.

Keywords: Micro-computed tomography, Enamel subsurface lesions, Mineral density, Remineralization, Functionalized tricalcium phosphate, Sodium fluoride

Backgrounds

Dental caries is a multifactorial disease caused by the damaging effect of acids on the enamel surface [1, 2]. The enamel is a relatively stable structure characterized by a dynamic balance between demineralization and remineralization [3, 4]. However, a disruption in this balance can lead to the development of demineralized lesions in the enamel. Remineralization is a repair mechanism that occurs naturally in tooth lesions. In this process, the

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State of the Art Enamel Remineralization Systems: The Next Frontier in Caries Management

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Keywords
Enamel caries · Remineralization · Non-fluoride remineralization · Fluoride booster

Abstract
The principles of minimally invasive dentistry clearly dictate the need for clinically effective measures to remineralize early enamel caries lesions. While fluoride-mediated remineralization is the cornerstone of current caries management philosophies, a number of new remineralization strategies have been commercialized or are under development that claim to promote deeper remineralization of lesions, reduce the potential risks associated with high-fluoride oral care products, and facilitate caries control over a lifetime. These non-fluoride remineralizing systems can be broadly categorized into biomimetic enamel regenerative technologies and the approaches that repair caries lesions by enhancing fluoride efficacy. This paper discusses the rationale for non-fluoride remineralization and the mechanism of action, challenges, and evidence behind some of the most promising advances in enamel remineralization therapies.

Dental caries pathophysiology is not simply a continual cumulative loss of tooth minerals, but rather a dynamic process characterized by alternating periods of demineralization and remineralization. Lesion progression or reversal depends on the equilibrium between demineralization-favouring pathological factors (cariogenic bacteria, fermentable carbohydrates, salivary dysfunction) and the protective factors (antibacterial agents, sufficient saliva, remineralizing ions) that tip the balance towards remineralization [Featherstone and Chaffee, 2018]. Remineralization can occur as a natural repair process where plaque/salivary calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions are deposited into crystal voids of the demineralized tooth structure, resulting in net mineral gain. The presence of free fluoride (F^-) ions in the oral environment can drive the incorporation of Ca^{2+} and PO_4^{3-} ions into the crystal lattice, with the ensuing fluorapatite mineral significantly more resistant to a subsequent acid challenge [ten Cate, 1999].

A better understanding of regenerative and physiochemical mechanisms has influenced the development of a number of innovative remineralization technologies that go beyond fluoride-mediated remineralization. While traditional fluoride-based remineralization re-

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Article

Remineralization of Demineralized Enamel and Dentine Using 3 Dentifrices—An InVitro Study

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Abstract: *Objectives:* To monitor the electrical resistance of artificially demineralized enamel and root dentine after exposure to different fluoridated dentifrices and, using transversal microradiography, to quantify remineralization. *Materials and methods:* This in-vitro blind investigation used 20 extracted teeth (four groups of five each). Each group was exposed to one test dentifrice [Colgate PreviDent (5000 ppm F), Colgate Winterfresh gel (1100 ppm F), Fluocaril Bi-Fluoré (2500 ppm F) and placebo (without fluoride)] three times daily for three minutes for 4 weeks. In between exposure to the test dentifrices, teeth were stored in a saliva storage solution. An Electrical Caries Monitor measured the electrical resistance at baseline and during the four-week test period at weekly intervals. The measurements were log transformed and Duncan's multiple range test applied. Remineralization was quantified using transversal microradiography. *Results:* Log mean (SD) electronic carries monitor (ECM) measurements in enamel at baseline and after 4 weeks of exposure to the test dentifrices were 4.07(1.53) and 3.87(0.90) (Placebo-Fluocaril), 4.11(1.86) and 4.64(1.43) (Colgate Winterfresh gel), 4.81(0.9) and 4.21(1.20) (Fluocaril Bi-Fluoré), and 4.60(0.88) and 3.76(0.9) (Colgate PreviDent). Corresponding measurements in dentine were 2.13(0.89) and 3.06(0.87) (Placebo-Fluocaril), 1.87(0.63) and 2.88(1.32) (Colgate Winterfresh gel), 2.47(1.20) and 1.65(0.60) (Fluocaril), and 2.16(0.00), and 2.34(1.07) for Colgate PreviDent. Lesion depth (μm) after microradiography in enamel was 100.1 (Placebo), 50.6 (Colgate Winterfresh gel), and 110.2 (Fluocaril, and 97.1 (Colgate PreviDent), and corresponding values in dentine were 169.7, 154.8, 183.7, and 153.5. The correlation of ECM and microradiographic parameters was negative ($p < 0.05$). *Conclusion:* Exposure of artificially demineralized enamel and root dentine to fluoridated dentifrices and saliva storage solution resulted in remineralization as follows: Colgate Winterfresh > Colgate PreviDent > Placebo-Fluocaril > Fluocaril Bi-Fluoré. Remineralization in teeth of the Placebo dentifrice group may be attributed to the presence of calcium and phosphate ions in the saliva storage solution.

Keywords: demineralization; enamel; white lesions; remineralization

RESEARCH ARTICLE

Weaker Dental Enamel Explains Dental Decay

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Abstract

Dental caries continues to be the most prevalent bacteria-mediated non-contagious disease of humankind. Dental professionals assert the disease can be explained by poor oral hygiene and a diet rich in sugars but this does not account for caries free individuals exposed to the same risk factors. In order to test the hypothesis that amount of amelogenin during enamel development can influence caries susceptibility, we generated multiple strains of mice with varying levels of available amelogenin during dental development. Mechanical tests showed that dental enamel developed with less amelogenin is "weaker" while the dental enamel of animals over-expressing amelogenin appears to be more resistant to acid dissolution.

OPEN ACCESS

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Competing Interests: The authors have declared that no competing interests exist.

Introduction

Dental caries is a leading cause of tooth loss in both developed and developing countries [1]. The disease affects billions of people and occasionally leads to lethality in both children and adults or important sequels, such as blindness [2–7]. To treat dental caries in the permanent dentition of children from developing countries by traditional amalgam restorative dentistry would require financial resources beyond the total health budget of these countries [8]. Children with poorer oral health status are more likely to experience dental pain, miss school, and perform poorly in school [9]. The aesthetic nature of untreated dental decay can at least indirectly compromise the child's self-esteem and social development [10]. Vaccine discovery efforts have focused on the bacterial species associated with dental caries, particularly *Streptococcus mutans*. Difficulties developing a vaccine against caries have included serological cross-reactivity between the heart tissue antigens and certain antigens from haemolytic *Streptococci* in some patients with rheumatic fever and lack of effectiveness of oral administrations. Intranasal route targets have been explored as well as alternative target antigens [11].

A proverbial belief among populations is that some people are born with teeth that are less resistant to dental caries ("weak teeth"), while others are born with teeth that are more resistant to dental caries ("strong teeth"). This difference is attributed to things as diverse as excessive milk consumption to infections and prolonged and/or repetitive use of antibiotics during

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REVIEW ARTICLE

Amelogenesis Imperfecta: A Review

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ABSTRACT

Amelogenesis imperfecta (AI) is a diverse collection of inherited diseases that exhibit quantitative or qualitative tooth enamel defects in the absence of systemic manifestations. This entity can present a variety of clinical presentation varies from hypoplastic, hypomaturative to hypocalcified which are the result of various genetic mutations. AI can present with a vast variety of features in single entity, so detailed knowledge of genetic mutations regarding AI, diagnostic, radiographic features, and different treatment modalities are mandatory while dealing these cases. We are presenting a review article on AI, mainly focused on its clinical presentation, genetic background, and its treatment modalities.

Keywords: Amelogenesis imperfecta, dominant, enamel, recessive

INTRODUCTION

Amelogenesis imperfecta (AI) is an inherited disorder which affects only the ectodermal portion of the teeth, i.e., enamel with the variable occurrence of approximately 1/700-1/14,000.[1-3]

Various classifications have been proposed based on the phenotype,[4,5] based on the clinical, microradiographic and histopathological findings,[6] based on the phenotype and mode of inheritance,[1,3,7-10] based on molecular defect, biochemical result, mode of inheritance, phenotype,[11,12] and based on molecular defect sub-classification of the AMELX conditions.[13] Most commonly accepted classification is the one being proposed by Witkop 1988[1] whichclassified AI into mainly 4 types, i.e., hypoplastic, hypomaturative, and hypocalcified type based on developmental stages of enamel and hypoplastic-hypomaturation with taurodontism [Table 1].[3]

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Hypoplastic AI occurs due to defect in enamel matrix deposition, i.e., the first stage of enamel formation. Clinically patient presents with thin enamel with yellowish-brown, rough or smooth, flat occlusal surfaces of the posterior teeth due to attrition, and with/without grooves and/pitting. The enamel will be thin, well mineralized and do not chip. Radiographically thin enamel but normal radiodensity will be seen. Defects in matrix formation with a disturbance in the differentiation or viability of ameloblasts will be seen in histology section.[14-16] Different types of hypoplastic AI are described in Table 2.

In hypomaturative AI Enamel, matrix protein is normal, but a defect in the maturative process of enamel's crystal structure so enamel matrix is immature. Clinically mottled yellowish brown with opaque discolored/snow colored crown can be seen, but normal in size and shape of the crown with Soft, poorly mineralized and discolored enamel which is easy to penetrate by the dental probe. The thickness of enamel may be normal, but radiodensity is less than of dentin radiographically. Microscopically alterations in enamel rod and rod sheath structures will be

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Review Article

Genetic and structural alterations of enamel and dentin- amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia

Abstract

Genetic alterations of enamel and dentin include different sub-groups recognized on the basis of their clinical appearance. Ameloblasts secrete three major enamel ECM proteins: AMEL (amelogenin associated with Amelogenesis Imperfecta phenotypes, ranging from hypoplastic to hypomineralized enamel), AMBN (ameloblastin) and ENAM (enamelin). They are localized within a cluster of genes critical to biomineralization mapped on chromosome 4q21. Hypoplastic enamel displays secretory defects (pitted, rough or local). Hypomineralized (with eruption pathology), hypocalcified types with mineralization defects, and hypomature enamel result to altered protein processing and crystallite maturation defects. They display a chalky appearance, orange, brown or white colour. Enamel is pigmented, snow capped. Dentin defects are classified into three types of Dentinogenesis Imperfecta (DGI, types I-III) and two types Dentin Dysplasia (DDs, types I and II). DGI type II was originally called hereditary opalescent dentin or Capdepont's teeth. Clinically, DGI-II is characterized by soft blue-brown, translucent teeth (opalescent teeth). Abnormal dentin obliterate the pulp chamber of DD type I. Genetically altered enamel and dentin structures allow significant insights on dental tissue genetic alterations, and consequently increase our understanding of the formation of normal dental tissues. The affected dental tissues involve gene mutations, translated into structural proteins and/ or implicated in the composition of dental tissues. This shed light on the cleavage of the constituent molecules of the ECM.

Keywords: proteins, molecules, phenotypes, dental tissues, gene mutations, heterogeneity, clinical appearance, autosomal recessive, basement membrane, maturation stage, enamel crystallites, gene

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Abbreviations: ECM, extracellular molecules; DD, dentin dysplasia; DI, dentinogenesis imperfecta; XLR, X-linked recessive; DSPP, dentin sialophosphoprotein; AR, autosomal recessive; AD, autosomal dominant

Introduction

The protein gene family includes extracellular molecules (ECM) proteins, responsible for dentin/bone coding (*DSPP, DMP1, IBSP, MEPE,* and *SPP1*), enamel (*AMEL, ENAM, AMBN,* and *AMTN*), as well as milk casein, and some salivary protein genes (Table 1). These molecules encompass inherited defects of dental enamel (AI) and dentin (DI and DD). They display both clinical and genetic heterogeneity. These groups include different sub-types recognized on the basis of their clinical appearance. Diseases affecting tooth structures have been classified into distinct tissues [enamel (AI) versus dentin (DI & DD), the specificity of the mutation (syndromic versus non-syndromic), and their pattern of inheritance [autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XLR)]. Mutations in the AMELX , ENAM , MMP20 and KLK4 genes are associated with specific AI types. Another series of gene mutations influence dentin structure and composition [dentinogenesis imperfecta (DI) and dentin dysplasia (DD)]. These mutated genes are implicated in defective dental tissues.[1-3]

Table 1 SCPP genes and ancestors

Gene symbol	Protein name	Protein distribution
Ancestor		
SPARC	secreted protein, acidic, cysteine rich (osteonectin)	skeleton
SPARCL1	secreted protein, acidic, cysteine-rich like 1 protein (high endothelial venule protein)	brain
SCPP		
DSPP	dentin sialophosphoprotein	dentin, bone
DMP1	dentin matrix acidic phosphoprotein 1	dentin, bone
IBSP	integrin-binding sialoprotein (bone sialoprotein)	dentin, bone
MEPE	matrix extracellular phosphoglycoprotein	dentin, bone

Demineralization–remineralization dynamics in teeth and bone

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