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Master Thesis
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„The Multifactorial Etiology of Dental Caries Disease“

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Abstract

In addition to all the studies on which scientists of all disciplines, especially dentists, base their research priorities, this literature review aims to provide a summary of the current state of knowledge on “The Multifactorial Etiology of Dental Caries Disease”.

The Background

The initial encouragement to research “The Multifactorial Etiology of Dental Caries Disease” came from observation of the prevalence of the dental caries disease, a common oral health problem in addition to periodontal disease. Although dental caries is preventable, it still affects people of all ages. In order to develop effective prevention and treatment strategies for dental caries, it is essential to have a comprehensive understanding of the underlying causes of this oral health problem.

The Aim

The objectives are to define the most recent theory, which examines the causes that contribute to the development of caries and assess its relevance to the understanding of this widespread oral health problem. A special focus is placed on the main factors of caries and by analyzing these factors, a comprehensive understanding of the development of caries will be obtained. By critically evaluating the existing literature and presenting research findings, approaches to the prevention of caries will be identified to made significant contribution to scientific community and the importance of oral health.

The Methods

This work presents a narrative research literature review focusing on the recent research literature on the etiology of dental caries disease. The research literature search strategy involved a manual search using the keywords "Dental Caries" and "Multifactorial Etiology" with the filter "Languages: English and German". This method included a wide range of sources to provide a comprehensive overview of the topic.

The Results

Through multifaceted approach, the definition, the etymology and the classification of caries was described according to the available literature. The main emphases of the research lied on the etiology, the factors causing the caries disease and the preventive determinants. Followed by Diagnostics and treatment of caries with respect to preventive measurements for prevention of the Caries risk and Improvement of oral health.

The Conclusion

According to the research, Miller's findings provided the basis for Keyes' concept of the 'Keyes loop', which illustrates the interaction of the three factors. König extended this theory by introducing the additional factor of 'time', which is now considered the modern theory of caries development. The development of dental caries is multifactorial and is influenced by several factors, including the host's anatomy and saliva, the bacterial microflora in plaque, diet and time. There are several co-factors contribute to the prevalence of dental caries including personal factors as well as oral environmental factors. The cornerstone of oral health prevention is based on three main principles: reducing plaque through good oral hygiene, fluoridation and a balanced diet. In addition, fissure sealants can be used to support these principles.

Keywords: Dental Caries, Multifactorial Etiology, Host, Dental Plaque, Diet, Demineralization

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1.Introduction

The motivation to deal with this topic initially resulted from observation the demineralization of dental hard tissues in the form of caries, a prevalent disease of the oral cavity alongside periodontitis. This led to a theoretical exploration of the Etiology of caries, laying the foundation for numerous theories aimed at explaining its development and understanding its causes over time.

There are numerous scientific studies that already deal with the Etiology of caries and its factors. The aim of this literature review is to investigate “The Multifactorial Etiology of Caries Disease”.

The objectives are as follows:
-Identifying the recent theory of caries development
-Identifying and analyzing the main factors causing the development of caries
-Identifying and evaluating the effectiveness of preventive measures to minimize the risk of caries.

Material and Methods

This thesis is a narrative research literature review of the recent research literature about the Etiology of dental caries disease. The research literature search strategy was manual research with the key words “Dental Caries” and “Multifactorial Etiology”, and the filter “languages: English and German” was applied. This method includes a wide range of sources to create an overview of the topic. Each article was reviewed for its relevance to this work, with particular focus on the most recent multifactorial theory to identify the most important factors and preventive measures, as well as evaluating the effectiveness of preventive measures to minimize the risk of caries. In particular, a comprehensive analysis of important historical contributions required significant effort to research and obtain the necessary references. In this thesis, the recent caries theory specifically analyzed, that provides the reader current knowledge of the etiology of caries. This theoretical foundation has led to the objectives of the study and the identification of the main factors that have determined the most current theory to date.

Importance

Caries remains a prevalent disease worldwide, affecting people of all ages. Due to its significant impact on oral health, it is essential to understand caries to be able to form effective prevention and treatment strategies. This requires a thorough understanding of the exact causes of caries.

A comprehensive review of the existing literature will provide strategies for the prevention and treatment of dental caries, with the aim of making an important contribution to the scientific community and the importance of oral health. The significance of health behavior and education in the context of oral prophylaxis is particularly evident in diseases such as dental caries, where preventive measures are of great importance. It is believed that a good understanding of oral health and the proper behaviors to prevent dental caries is crucial. Awareness-raising is essential, but can only be achieved if there is a clearer definition of health and disease. A comprehensive understanding of health is essential to effectively manage diseases such as dental caries.

2.Anatomy and the Biochemistry of Teeth

The visible crown and the anchored root are the two main parts. The crown, which is covered with a hard layer of enamel, is the top part of the tooth, above the gum line. The root, that is located in in a socket called an alveolus, which is a part of the jaw bone below the gum line, gives the tooth its stability (Schuhmacher et al., 1990). The transition area between the crown and the root is called the cervix, which is a critical area that can be prone to gum recession if not properly cared for. Gum recession over time can expose the neck of the tooth, causing potential problems (Al Omari et al., 2007). The tooth is made up of a number of different layers, each designed to function in a different way. These layers include enamel, dentin, pulp and cementum, which work together to protect and support the structure and function of the tooth. The following is a description of these layers, working from the outside inwards.

The following graphic visualizes a cross sectional view of the anatomical structure of the molar tooth.

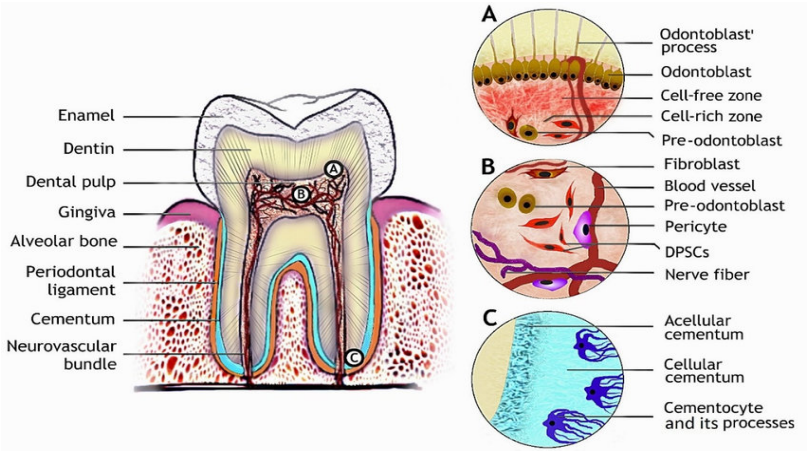


Fig. 1 Anatomy of the tooth (Juliana Baranova et al., 2020)

Tooth structure and dental tissues with the respective stem cell populations. (A) The odontoblast niche is bordering dental pulp beneath the dentin with odontoblast processes projecting towards enamel. (B) Diverse cell populations are found in dental pulp, DPSCs, which can give rise to odontoblasts. (C) Cementocytes are residing in the lacunae of cellular cementum at root apex with their cellular processes projecting towards the periodontal ligament.

Dental enamel, the hardest tissue in the human body, makes up about a quarter of the total mass of a tooth. It is thickest at the occlusal surface of the tooth, where it is approximately 2 to 2.5 mm in thickness (Oeschger, 2006). The hardness of the enamel decreases from the surface to the enamel-dentine junction and varies between MH 5 and MH 8 on the Mohs scale, which measures mineral hardness (Taatz, 1980; Schuhmacher et al., 1990; Nanninga et al., 1996). A higher hardness of the enamel indicates a higher density of mineral salts in the basic organic substance (Klussmann, 1936; Oeschger, 2006). Resistance to acid decalcification is increased by a higher content of fluorapatite in the crystal structure of the enamel. The main component of enamel is hydroxyapatite -$Ca_5(PO_4)_3OH$ (Rheinwald, 1956). Its inorganic composition consists of calcium and phosphate, while its organic composition consists of proteins (Schmidt, 1974; Oeschger, 2006). Enamel maturation is usually complete by the age of 20 (Stößer, 1993). The enamel is the product of the ameloblasts and after this stage it can no longer be repaired by the cells (Starck, 1979). Blood and saliva contain dissolved calcium phosphate, which constantly renews the lost enamel. However, it is still unclear how this biomineralization process works in detail (Donner, 2006).

The main function of the **cement** surrounding the tooth root is to anchor the fibers of the periodontium to the alveolar bone so that the tooth is softly cushioned under load (Schuhmacher et al., 1990). Dental cement organically consists of collagen fibers and is chemically similar to bone (Meyer, 1951; Riethe, 1985; Taatz, 1980).

The main component of the tooth is the **dentin** (Substancia eburnea), which has a Mohs' hardness of 3 to 4 (Nanninga et al., 1996). Dentin is externally surrounded by enamel in the crown area and by dental cement in the root area and internally encloses the pulp (Meyer, 1951). It consists of 70% inorganic material including calcium and phosphate, but to a minor amount, approximately 2/3 of it. Collagen makes up about 15-20% of the organic matrix. Non-collagenous proteins make up 1-2%, while the remaining 10-12% is water. Magnesium, carbonate and fluoride are common minerals, along with some microelements. As a result, it is softer than enamel, making it more susceptible to caries (Hellwig et al., 1999). The odontoblasts in the pulp are capable of regenerating replacement dentin. According to (Riethe, 1985), the pulp tissue provides nourishment for the odontoblasts, which actively participate in dentin formation (Taatz, 1980).

From the functional point of view, **dentin and pulp form a functional unit**. The dentin is penetrated by the cell processes of the odontoblasts. These are the pulp cells that line the pulp cavity. Each odontoblast process terminates in the dentinal tubule, which runs vertically in a slightly curved course

from the dentin-pulp junction straight through the dentin to the enamel-dentine junction (Schuhmacher et al., 1994). The outermost layer at the cementoenamel junction is called the mantle dentin and has a lower degree of mineralization than the apically located circumpulpal dentin. The hypomineralized predentin is located at the junction with the pulp, immediately adjacent to the odontoblast layer (Schröder, 2000). Dentin can be continuously formed by the odontoblasts throughout life (secondary dentin). Tertiary dentin is formed after tooth eruption by renewed production by odontoblasts (secondary odontoblasts) in response to mild stimuli such as abrasion, wear, erosion, trauma, incipient dentin caries and some therapeutic procedures (Ten cate et al., 2003)

3.First Evidence of Caries Cavities

Dental caries is a common disease in humans, affecting almost every adult during their lifetime. The incidence of caries has been used to study changes in human diet over time, with a suspected link between the incidence of tooth decay and a high-carbohydrate diet. Caries is neither limited to humans nor is it a new phenomenon (Adler et al., 2017; Lovell, 1991; Kemp, 2003; Towle et al., 2019).

The fact that caries has already been detected in an extinct mammal shows that this disease has existed for a long time and is not limited to humans (Towle et al., 2019). A study published in 2021, showed that caries was already present in a small mammal belonging to an extinct group of relatives of all modern primates, including humans. This finding thus marks the earliest known case of tooth decay in a mammal. Microsyops latidens, a mammal that existed about 54 million years ago and lived to about 544,000 years old, probably used to live on trees. Although only a few skeletal fossils have been found, palaeontologists have uncovered thousands of jawbones with teeth (Keegan et al., 2021).

About 7.5 % of the fossils showed cavities, in one section of the fossil record even 17.24 %. This is an indication of changes in the diet of M. latidens. The strong variation in caries frequency suggests that M. latidens increasingly fed on fruits or other sugary foods (Holloway, 1983), whereby it is assumed that the food supply changed due climatic fluctuations (Keegan et al., 2021; Bernard, 2021).

Very interesting is the observation by Keegan R. Selig that the caries holes in the teeth of Microsyops latidens were always in the same place and had a smooth, rounded contour. The uniform features suggest that the holes are actually caries caused by bacterial decomposition of the tooth and not accidental damage (Keegan et al., 2021).

"These fossils have been lying around for 54 million years, and a lot can happen in that time," says Keegan. "I think most people assumed that these holes were some kinds of damage that occurred over time, but they always occurred in the same place on the tooth and had this smooth, rounded curve throughout." (Keegan et al., 2021).

Fig. 2 *" The structure of the molars changed as the number of cavities increased, suggesting a high-sugar diet."* (Keegan Selig)

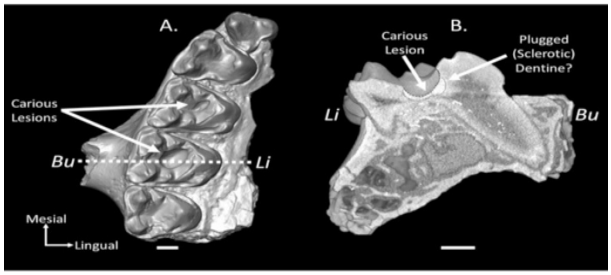


Fig. 3 *"Micro-CT scans were used to find cavities and examine them."* (Keegan Selig)

4.Caries

4.1. Definition of Caries

Dental caries is defined as a microbiological disease of the calcified tissues of the teeth, characterized by excessive demineralization of the inorganic part and destruction of the organic substance of the tooth, often leading to cavities (Sbordone et al., 2003; Schmidt, 1974).

4.2. Etymology of Caries

The word "caries" originates from the Latin word meaning "rotting, putrefaction". In a medical context, caries is defined as the process of tooth decay caused by bacterial activity and acid formation in the mouth. The destructive nature of this disease, which can lead to progressive loss of tooth substance, is reflected in the etymology of the word.

The use of the word "caries" for teeth has been criticized by proponents of various caries theories because "caries" is in fact "cavitation". The typical signs of decay, such as an alkaline reaction and foul odor, are not present in a cavity where the carious process is actually taking place. Instead, the carious dentin shows an acidic reaction and an acidic odor (Miller, 1889). An appropriate term for the process of mineral dissolution might be erosion. The term " decay " does not accurately describe the nature of dental caries. Therefore, "caries" should not be interpreted as "decay" (Rheinwald, 1956).

The term "dental caries" was first defined at a time before fully understanding the nature and causes of dental caries. The destructive process of dental caries proceeds in a unique way that cannot be classified in the categories associated with general pathology and has no analogy in any other disease (König, 1987).

4.3. Classification of Caries

Caries can be categorized according to four factors:

- Morphology (according to anatomical localization)
- Dynamics (according to the progression)
- Severity (according to severity of the lesions)
- Chronology (according to age-specific occurrence)

4.3.1. Classification According to Morphology

4.3.1.1. Occlusal Caries and Smooth Surface Caries

The different surfaces of the tooth can be divided into two morphological types. While type I refers to lesions on fissures, pits and occlusal surfaces, type II is characterized by lesions on interproximal and gingival or cervical surfaces (Summit et al., 2001). Pit and fissure caries affects the molar, premolar and palatal surfaces of the maxillary anterior teeth. As these irregular surfaces are more susceptible to lesions due to their lack of self-cleaning ability, type I caries is also more common than type II caries, which occurs at mesial and distal contact points and cervically at the enamel-cement junction (Ash & Nelson, 2003).

4.3.1.2. Root Caries (Cement Caries)

Root caries, also known as cement caries or cervical caries, occurs when the dentin in exposed tooth necks or roots lacks enamel protection, making it more susceptible to the caries process. Root caries starts on the mineralized cementum and is based on a different bacterial spectrum than enamel caries, as the organic content of the root and dentin is higher. It most commonly affects the buccal root surfaces of molars and premolars, whereas canines and incisors are less commonly affected. Root caries mainly affects the elderly due to age-related degeneration of the gums and patients at risk of periodontitis because part of the root has been exposed due to recession or deep pockets in the gums (Galan et al., 1993). Such roots already have a history of disease when root caries begins because the root dentin has probably already reacted to decalcification of the cervical area (cervical caries) due to recession (Banting, 2006)

4.3.2. Classification According to Dynamics

4.3.2.1. Incipient Caries

Incipient caries, characterized by white spots on the teeth, is an early stage of caries in which demineralization of the enamel has occurred without visible lesions or organic changes (Nikiforuk, 1985). The whitish areas become more visible when the tooth is air dry. These early lesions may also have brown spots, indicating arrested caries. Early caries primarily involves mineral loss rather than bacterial invasion and is therefore a chemical rather than a structural problem. A bitewing radiograph may show small radiolucent spots in the enamel at this stage (Brudevold et al., 1956). It's important to note that the presence of white spots does not necessarily indicate the need for filling therapy.

4.3.2.2. Rapidly Progressing Caries

The rapid and uncontrolled progression of caries, even in areas normally considered relatively caries-free, such as the proximal and cervical surfaces of anterior teeth, including mandibular incisors, is referred to as 'rampant caries'. Such dynamic caries is characterized by an increase of ten carious lesions per year. This type of caries is most common in the primary dentition and in the permanent teeth of 11–19-year old's (Brudevold et al., 1956).

4.3.2.3. Arrested/Inactive Caries

Inactive carious lesions are those that have become static, arrested in their progression and may even begin to remineralize. It has been clinically demonstrated that advanced carious lesions can be stopped completely by adjusting the oral environment to slow down the process. Backer Dirks (1966) even showed in his studies of 184 maxillary first molars that remineralization was observed in over 50% of the 72 white spots, no change in 36% and development of deeper lesions in only 14% (Dirks 1966). Clinically, arrested caries in dentin appears as brown pigmentation and hardening of the lesion.

4.3.2.4. Secondary Caries

Secondary caries is the recurrence of caries at a previously treated carious area, at the margin of a filling or at the margin of a restoration, such as the margin of a crown. Secondary caries occurs mainly when there is a marginal gap at the edge of a restoration to which plaque can adhere. The most common cause of marginal caries is (micro-)leakage at the margins of crowns or fillings associated with poor oral hygiene (Sonis et al., 2003). This may be new caries or the remnants of caries that has

not been completely removed. Primary caries would then be the appearance of caries in a place that was not previously affected by caries (Silverstont, 1983).

4.3.2.5. Radiation Caries/ Xerostomia-induced Caries

Damage to the salivary glands during head and neck radiotherapy leads to dry mouth, known as xerostomia which is a well-known side effect of radiotherapy for oral cancer. These patients develop rapidly progressing caries, highlighting the importance of saliva for tooth preservation. There are changes in salivary flow, salivary and serum proteins and a shift towards cariogenic microflora. The first lesions appear in the first three months after radiotherapy. Other causes, such as tumors in the head and salivary glands, autoimmune diseases and antisialagogues, can also lead to xerostomia (Nikiforuk, 1985). The risk of so-called radiation caries (caries radiatio) is extremely high in these patients due to the loss of the neutralizing and remineralizing effect of saliva.

Dry mouth leads to a continuous loss of enamel minerals through radio xerostomia and increases the risk of radiation caries (Neville et al., 2002).

4.3.3. Classification According to Severity

4.3.3.1. Initial Caries

The earliest stage of tooth decay is called initial caries. In this stage, tooth enamel starts to demineralize. The tooth enamel becomes soft and porous. Characteristics of initial caries include white spots on the tooth surface, a reversible stage and no cavities as the damage is limited to the outer layer of enamel (Nikiforuk, 1985; Brudevold et al., 1956).

4.3.3.2. Moderate Caries

In moderate caries, caries penetrates deeper into the tooth, leading to symptoms like pain, sensitivity, and discoloration. This stage is marked by white spots, superficial lesions, cavities, mild pain, and gum issues. The proximity to the nerve can heighten sensitivity to hot or cold stimuli (Nikiforuk, 1985).

4.3.3.3. Advanced Caries

Advanced caries is a stage of tooth decay between the early stages and severe damage. At this stage, the caries has progressed deeper into the tooth and caused visible damage to the tooth surface. Then there is a higher risk of complications such as infection, which can affect the inside of the tooth. In these cases, the caries can reach the dentin close to pulpa, which can lead to inflammation of the

tooth's nerve. This can cause severe pain and infection inside the tooth, visible cavities, dark discoloration, sensitivity, bad breath or taste (Nikiforuk, 1985).

4.3.3.4. Severe Caries

Severe tooth decay refers to advanced tooth decay that has progressed to the point where it has caused significant damage to the tooth structure. This can lead to pain, infection and possible tooth loss if left untreated. This type of caries can look different depending on the progression of the caries and individual circumstances. Typical signs and symptoms of severe caries can include: deep cavities, dark discoloration, tooth sensitivity, tooth destruction, pain and infection and swelling or abscesses are possible signs (Nikiforuk, 1985).

4.3.4. Classification According to Chronology

4.3.4.1. Early Childhood Caries (Nursing Bottle Caries)

Lesions of the primary teeth typically occur in the first two years of life and primarily affect the upper incisors, as these are the teeth that are most heavily exposed to food mucus due to their anatomical position. While the spread reaches the upper and lower molars, the lower incisors are usually not affected due to the rinsing by the salivary gland secretions and the cleaning of the teeth by the tongue movement (Ripa, 1978). Atypical feeding is one of the main causes in these children, to which the addition of syrup, sucrose, honey or other sweeteners in infant formula, pacificators dipped in honey and consumption of sweetened fruit juices contribute (Derkson et al.,1982). It has also been confirmed that prolonged night-time breastfeeding also leads to increased caries rates (Preston et al., 1977).

4.3.4.2. Adolescent Caries

Adolescent caries is the term used to describe acute caries between the ages of 11 and 19. Lesions on more caries-resistant teeth, a small lesion in the enamel with severe undermining of the enamel, rapid progression and extensive dentin involvement are characteristic of this type of caries (Brudevold et al., 1956). The speed of spread does not allow an adequate pulp response (little to no secondary dentin). The untreated carious lesion progresses through the enamel, followed by the dentin and finally through the pulp, leading to a periapical abscess and, without adequate treatment, to inflammation of the surrounding soft tissue with edema (Nikiforuk, 1985).

5.Etiology of the Caries Disease

5.1. Dentistry´s Contribution to the Etiology of Caries

Various theories have been found in the records of ancient peoples attempting to explain the characteristic toothache. The Latin word 'caries' is derived from the Latin word for rotting or putrefaction and should describe the state of decay caused by tooth caries. The similarity with the Greek word for death, kēr, could indicate that people early on recognized the serious consequences of untreated caries (Pickerill, 1924).

The current state of knowledge on the causes of caries is a long way from its beginnings. However, researching the causes of caries has been, and continues to be, an interdisciplinary endeavor. Because caries is such a broad field of research, scientists from many disciplines have been involved in the investigation of its causes, in addition to dentistry. These include microbiology, biochemistry, nutrition, epidemiology and genetics, all of which have made significant research contributions to caries.

It is emphasized that the benefit of modern medicine, including dentistry, lies in understanding the causes of this disease spectrum and the associated disease risks. This is supported by quotes from Friedrich and Widemann who underline the importance of knowing the causes of disease to provide effective prevention (Friedrich, 1983; Wiedemann, 1993).

5.2. The Chemo-Parasitic Theory According to Miller

In contrast to the speculative hypotheses of the past, William D. Miller put forward a well-founded theory that is still relevant today and introduced it into dental research (Riethe, 1985). His research was strongly influenced by the ideas of Robert Koch (König, 1987).

His Chemical parasite theory assumed that most bacteria were aerobes, as anaerobes were not well known at the time (Pilz, 1980). Since Miller's time, our understanding of the bacterial composition of the mouth has evolved and we now know that anaerobes are actually present in greater numbers than aerobes.

It is worth noting that Miller distinguished between enamel caries and dentinal caries, considering them to be separate processes. He regarded enamel caries as a purely chemical process in which the enamel is destroyed by chemical decalcification. Miller, on the other hand, regarded dentinal caries

as a chemical-parasitic process in which the decalcification of dentin is caused by acids produced by bacteria (Fleischmann, 1921). This process involves two distinct stages: the decalcification of the tissue and the dissolution of the softened residue. However, the second stage is absent in enamel caries; because *"the decalcification of enamel means its complete destruction"* (Miller, 1889).

First stage of caries

According to Miller the origin of the acids necessary for enamel dissolution can be easily determined by studying the fermentation processes (Pilz, 1980). Fermentation processes can be traced to the origin of the acids needed to soften enamel at this stage. Miller pointed out that starchy and sugary food residues remaining in carious lesions form acids through fermentation. In particular, lactic acid, which is produced primarily by the fermentation of carbohydrates in the oral cavity, plays a crucial role. Lactic acid is known to rapidly attack and decalcify dental tissues. This leads to the loosening of the enamel prisms by the acids, the origin of which, according to Miller, is clearly attributed to the fermentation processes (Miller, 1889).

Second stage of caries

Miller described the involvement of fungi in the decomposition of dentin as part of the caries process. After softening of the dentin, fungi begin to attack the dentin. The fungi are directly involved in this process as they penetrate between the loose enamel prisms, possibly splitting them further and destroying the remaining organic substance. *"The splitting fungi have no direct effect on normal enamel"* (Miller, 1889), indicating that they can specifically target and affect specific structures within the dental tissue. This insight highlights the importance of the microbial flora in the oral cavity for the development and progression of caries. Miller's identification of the involvement of fungi in the decomposition of dentin contributes to a deeper understanding of the complex interactions between microorganisms such as fungi and dental tissue in the caries process (Miller, 1889).

Miller's findings that microorganisms in the oral cavity produce acids through the enzymatic breakdown of carbohydrates in food provided an important clue to the potential role of acids in the development of caries. However, definitive proof of this cause was still missing and would not be found until many decades later. This uncertainly led many scientists to develop and discuss alternative theories about the origin of caries, delaying the search for

1. the identification of the real cause of caries and thus
2. effective caries prevention

W.D. Miller's chemical parasitism theory was a major contribution to dental research and helped to deepen the understanding of the causes of caries. Although the theory has been further developed by modern knowledge and research, it remains an important milestone in the history of dentistry (Riethe, 1985).

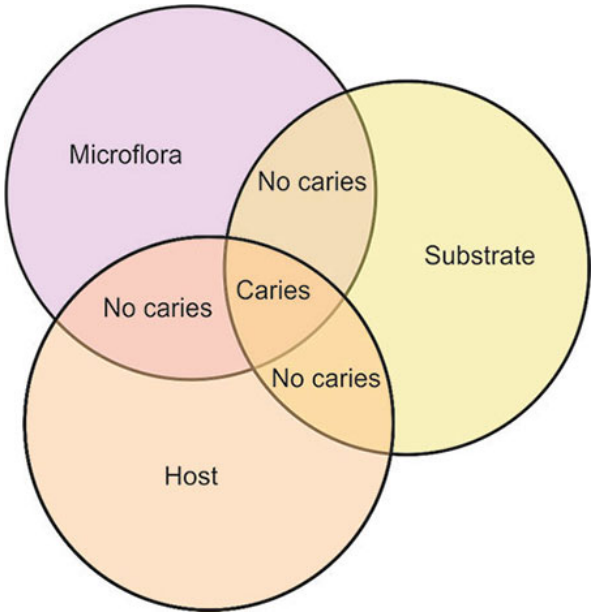
5.3. The Etiology of Caries

There are many theories regarding the etiology of caries disease. The slightly modified form of the 'chemo-parasitic theory' formulated by Miller in 1898 forms the basis of the multifactorial etiology of caries development. In 1889, Miller formulated the theory that caries is caused by microorganisms in the oral cavity that produce acids through the enzymatic metabolism of carbohydrates in food, and these acids attack the hard tissues of the teeth (Miller, 1893).
In 1954, Orland et al. provided conclusive evidence of this in rats cultured in a germ-free environment. In agreement with Pasteur's view that life in higher organisms is not possible without symbiosis with microorganisms, they noted:

„Findings indicated that (22) rats (Rattus norvegicus albinus) reared under germfree conditions remained entirely free of even microscopically demonstrable dental caries. Of (39) conventional control rats, possessing the usual mixed microbial populations, (38) developed carious lesions when maintained on the same kind of dietary regime as the germfree animals. It is deduced from this evidence that dental caries in the rat is not possible in the absence of microorganisms" (Orland et al., 1954).

In 1962, Keyes developed the concept of the 'Keyes Loop' or 'Keyes Circles' to illustrate the complex interactions between different factors in the development of caries (Arathi, 2012). According to Keyes, caries can only occur through the interaction of three factors: host organism (tooth) + diet + microorganisms (Featherstone, 2004). This schematic is still widely used in dental education and research today.

König added a fourth factor, time, to the three-factor circle, proving that demineralization of the tooth enamel, known as demineralization, only occurs if the acid remains on the tooth surface long enough (König, 1987).



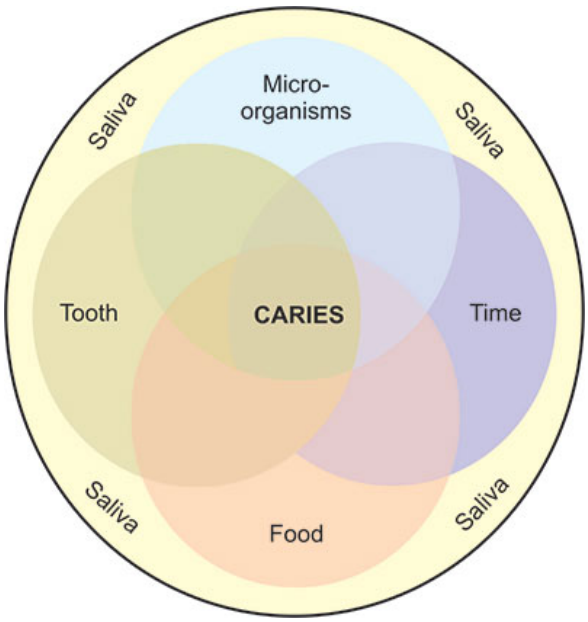


Fig.4 Etiology According to Keyes (Arathi, 2012) **Fig.5** Etiology According to König (Arathi, 2012)

An important demonstration of the fourth caries factor, time, was provided by the extensive Swedish Vipeholm study. The Vipeholm study was a controversial study conducted in Sweden in the 1940s and 1950s. The aim of the study was to investigate the relationship between sugar consumption and the development of tooth caries. Mentally handicapped people in a state institution called Vipeholm in Lund were selected as subjects. This study laid the foundation for the understanding that it is not the amount of sugar, but the length of time that carbohydrates remain in the mouth that is crucial for the development of caries (Berlin 1953). During the five-year study, all 436 participants received four main meals in the first nine months. A control group and six test groups were then formed, in which different sugars were consumed at different times and in different amounts. The effects were minimal in those who consumed sugar at mealtimes. However, a significant effect was observed in the group that consumed 24 caramel sweets as a snack, as the caramel remained on the teeth for a long time. This observation led to the identification of the fourth caries factor in the Vipeholm study (Gustafson et al., 1954).

This extended model, which takes into account the interactions between the factors, is often regarded as the basic model for the development of caries. The study shows that caries can only be caused by a combination of these four factors (Zimmer, 200).

In summary, in addition to the factors that act as defense mechanisms in the oral cavity, there are also many metabolic products that could cause damage to the tooth - such microbial diversity is otherwise only found in the skin and intestine, which have regenerative capabilities, whereas tooth enamel is non-regenerative and therefore more susceptible to damage such as caries. It can be concluded that a tissue such as tooth enamel has been placed in a relatively hostile environment such as that found in the oral cavity. Caries is therefore a tissue-specific, localized disease of dental hard tissue caused by metabolites of oral microorganisms (Nikiforuk, 1985). The definition of caries as *"a disease of bacterial origin leading to demineralization and the formation of a cavity"* (Vanin, 2005) emphasizes the importance of chemo parasitic theory in explaining the development of caries. The interaction between oral microorganisms, their metabolites and tooth enamel play a central role in the pathogenesis of caries. This has important implications for the prevention and treatment of this disease.

6.Pathogenesis and Pathophysiology of Caries

6.1. The Host as a Factor

An important factor influencing the development of caries is the individual characteristics of the tooth, including its location, morphology, structure, composition and post-eruptive age. The crystalline structure and chemical composition of the enamel are particularly important. In addition, saliva plays a crucial role as its composition can vary significantly and has a considerable impact on dental health (Klimek et al., 1999; Larsen et al., 1999).

6.1.1. Anatomy of the Teeth

In addition to tooth enamel and saliva, there are other individual factors that play a role in the onset and development of dental caries. These include the shape and position of the teeth, the structure and composition of the enamel, the amount and composition of saliva, and immunological conditions (Klimek et al., 1999; Larsen et al., 1999). Difficult mechanical cleaning due to tooth shape and position facilitates plaque accumulation, increasing the risk of caries (Marsh et al.,2002).

The caries incidence of permanent teeth, as determined by Künzel in 1997, shows that molars are most susceptible to caries due to their numerous fissures and pits. This is because plaque can accumulate more easily in these depressions, promoting the development of caries. In second place are the upper incisors, followed by the upper and lower premolars. The least susceptible to caries are the upper canines and the lower incisors (Künzel, 1997). Also noteworthy is the difference in caries

prevalence between permanent and primary teeth. In permanent teeth, fissures and pits are more likely to be affected by caries, whereas in milk teeth, the smooth surfaces of the teeth are more susceptible to caries. This may be due to structural differences in the tooth surfaces and possibly the enamel (Anderson, 2002; Brown et al., 1995, De Grauwe et al., 2004).

6.1.2. The Enamel

The tooth is covered with a layer of enamel that protects the underlying dentin and the pulp from external influences. In a permanent tooth, the enamel layer can be up to 2.5mm thick on the occlusal surface. The enamel becomes thinner towards the cementoenamel junction, where it meets the root cementum, which covers the root surface (Schröder, 2000).

Enamel is the hardest, most abrasion-resistant, but also the most porous substance in the human body and is produced by specialized cells called ameloblasts. These cells, of neuroectodermal origin, differentiate from the inner enamel epithelial layer, which develops from a single layer of highly prismatic epithelial cells. In the region of the dental papilla, this differentiation leads to cell proliferation into odontoblasts and the formation of dentin. Enamel is acellular and avascular and is therefore incapable of regeneration or repair after microbial attack. The hardness of enamel ranges from approximately 250 KHN at the cementoenamel junction to 390 KHN at the enamel surface (Schröder, 2000). KHN means Knoop Hardness Numbers, that is a measure of material hardness determined by a test developed by Frederick Knoop. Due to differences in mineral density, the hardness of enamel decreases from the tooth surface to the cementoenamel junction. The relative density of enamel ranges from 2.8 to 3.0, depending on maturity, sampling area and chemical composition (Schröder, 2000; Buddecke, 1981).

The melting point is quite high at 1620°C, but the main disadvantage of enamel is its solubility in acids. This is due to hydroxyapatite, which makes up 95% of the main component of enamel (Hellwig et al., 1999). Hydroxyapatite is an inorganic compound consisting of calcium and phosphate in a framework, and also contains magnesium, sodium, proteins and fats. Its crystal structure is the so-called apatite structure. Other apatite structures such as fluorapatite and carbonated apatite are also present in tooth enamel, although fluorapatite has a much more stable crystal framework than hydroxyapatite (Aobat, 2004; Featherstone, 2000). Carbonated apatite is less resistant to caries than hydroxyapatite. It also correlates with the density of the enamel (Buddecke, 1981). In areas with high carbonate and magnesium content, there is a significant decrease in enamel density. The remaining

enamel components can be divided into other organic materials of approximately 1 to 2% and water of approximately 4% by weight and 6% by volume (Lundeen et al., 1995).

Apatite crystals in mature enamel appear as slightly flattened, approximately hexagonal rods. One hundred of these apatite crystals form the cross-section of an enamel prism and are embedded in a jelly-like, unstructured organic matrix (Schröder, 2000). The enamel layer formed at the end of amelogenesis is harmless and corresponds to the upper 20-80µm (Lehmann et al., 2000). It is harder and less acid soluble than the enamel immediately below it. Although enamel has a very dense structure, it is permeable to certain ions and molecules, allowing partial or complete penetration. The passage appears to occur through hypomineralized structural components. Water appears to play an important role as a transport medium in the small intercrystallite spaces (Koulourides, 1966; Lundeen et al., 1995). As enamel ages, its permeability decreases, while remaining fundamentally permeable. This decrease is also known as the maturation of the enamel. In an acidic medium, enamel is soluble, although dissolution does not occur equally. The solubility of enamel progresses at different levels from the enamel surface to the enamel-dentine junction. If fluoride is present during enamel formation or is applied locally to the enamel surface, the solubility of the surface enamel is reduced (Schröder, 2000).

Microdefects of the tooth surface and certain abnormalities of the dental hard tissue that promote increased plaque retention can also cause an increased risk of caries if oral hygiene is inadequate (Schröder, 1997). However, it has been shown that hypoplastic (poorly mineralized) teeth do not have an increased risk of caries compared to physiologically mineralized teeth (König, 1992). A significant link between the chemical composition of dental hard tissue and caries susceptibility has not been evidenced (Nikiforuk, 1985). Therefore, it is the ability of plaque to accumulate rather than the histological or chemical composition of dental hard tissue that promotes the development of caries. However, the fluoride content of the superficial enamel structure has been shown to be beneficial in maintaining oral health (Featherstone, 2006). To prevent caries lesions, the mechanical cleaning of the tooth surface, and therefore the removal of plaque, is essential. Regular professional dental cleaning significantly reduces the risk of caries (Axelsson et al, 1993). Oral hygiene habits not only vary from person to person, but also change over the course of a lifetime.

6.1.3. The Saliva

The role and importance of saliva in caries has long been unclear. In 1912, Dr Joseph Head of Philadelphia first reported the enamel-hardening properties of saliva (Head, 1912). Saliva is an important protective mechanism for the teeth and oral mucosa and maintains the environmental balance in the oral cavity. Various functions such as tasting, speaking, chewing, carbohydrate metabolism and swallowing would not be possible without saliva (Nikiforuk, 1985). A large number of microorganisms are removed from surfaces and swallowed with saliva. Saliva also contains minerals that are essential for the regeneration of tooth enamel (König, 1999). Changes in consistency or viscosity are therefore associated with an increased risk of caries, as well as a general reduction in quality of life when salivary flow is reduced, for example due to medication in older age. It can make eating, speaking and swallowing difficult (Nikiforuk, 1985). Dental caries, periodontal disease and other soft tissue diseases are also associated with reduced salivary flow.

6.1.3.1. The Composition

Saliva is mainly produced by three large paired salivary glands: the parotid, sublingual and submandibular glands, in addition to small solitary glands in the labial, buccal, palatal and lingual mucosa. Each gland secretes saliva with a distinctly different composition.

The submandibular gland contributes approximately 65% of resting saliva, the parotid gland 20%, and the sublingual and minor salivary glands each contribute 7-8% of total salivary secretion (Dawes, 1990). When stimulated, the parotid gland's contribution to the total salivary volume increases to approximately 50% (Hanson, 1961; Shannon, 1968; Dawes, 1990).

There is continuous resting secretion, even in the absence of external influences, probably due to the uninterrupted activity of the salivatory nuclei in the brainstem. A total of about 0.5-1.5 liters of saliva is secreted daily (Avery et al., 2002; Humphery et al., 2001), with variations in the amount of saliva secreted throughout the day. The normal flow rate is about 0.3-0.4 ml/min, while during stimulated saliva production it averages 1-3 ml/min, with a maximum of 7 ml/min. Unstimulated saliva follows a circadian rhythm, with a maximum in the afternoon and a decrease in saliva production during the night, with a typical salivary volume of only about 20 ml (Humphery et al., 2001), The amount of resting saliva, and therefore its pH and buffering capacity, can be slightly increased by regularly chewing hard, chewy foods or chewing gum for several weeks. As a result, the flow rate of stimulated saliva also increases slightly. This is probably due to an increase in the size of the salivary glands (Jenkins et al., 1989; Dawe, 1990; Dodds et al., 1991)

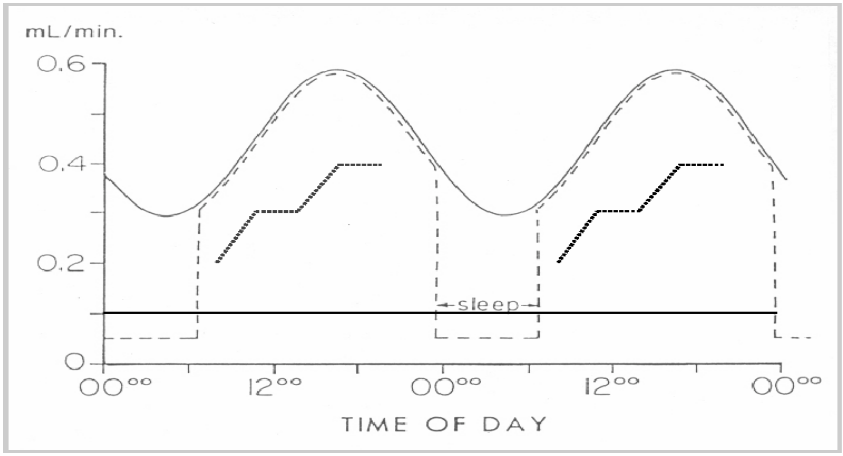


Fig. 6 The Circadian Rhythm in Unstimulated Salivary flow rate (Flink, 2007)

In the mouth, saliva mixes with plaque fluid, sulcular fluid, cells and epithelial debris from the mucous membranes. It also contains microorganisms and the metabolites they produce (König, 1987). Saliva quantity and composition depend on many other factors such as chewing activity, stimulation of taste receptors or other sensory nerves. Psychological and emotional factors, such as stress, also affect salivary flow. Certain medications, such as psychotropic drugs, systemic diseases, or radiotherapy for head and neck, leading to xerostomia. 99% of total saliva consists of water and *"contains in liquid form all dissolved mineral components of dental hard substances (appetites), ... calcium, phosphate, and insufficient ... fluoride ions."* Furthermore, approximately 5 g/l, or to be more precise, between 3-8g/l of secreted substances are contained in total saliva, of which one-third is inorganic and the rest is organic substances (König, 1991; Schwenzer et al., 2000)

The **organic components** consist of salivary enzymes, enzymes of bacterial origin, immunoglobulins, glycoproteins such as mucins, and serous secretions. Salivary enzymes include alpha-amylases, a digestive enzyme essential for breaking down carbohydrates into simpler sugars; lysozymes, which have a lytic effect on bacterial cell walls, making them bactericidal; and lactoferrins, (Van Niuw et al., 2002) which bind iron and prevent Fe(III)-dependent growth of microorganisms such as Candida albicans and Escherichia coli (Van Niuw et al., 2002). Another salivary enzyme is lactoperoxidase (LPO). Together with hydrogen peroxide and thiocyanate, which is absorbed from the blood into the oral cavity via the salivary glands, hypothiocyanate is formed. This compound is bactericidal by inhibiting bacterial glycolysis (Hannig et al., 2007). The most common immunoglobulin produced in the salivary glands and directly secreted is immunoglobulin A. IgG and IgM are present in smaller amounts. Mucins support the protective function of immunoglobulins and cover the mucous membranes and tooth surfaces (König, 1987; Van Niuw et

al., 2002). Despite the presence of various antibacterial components, a large number of microorganisms can thrive in the oral environment. The function of the antibacterial factors in saliva is poorly known, but it is assumed that they prevent the colonization of pathogenic bacteria (Nikiforuk, 1985).

Inorganic substances in saliva are primarily sodium, calcium, phosphate, chloride, magnesium, bicarbonate, and fluoride. Saliva is a solution that is supersaturated with calcium and phosphate. Because of its high ion content, saliva is also known as an electrolyte (Buddecke, 1981). Some of these ions form saliva's important buffering systems that protect against acid attacks, namely bicarbonate and phosphate buffers (Featherstone, 2000). Buffers are mixtures of a weak acid or base and its salts. They convert strongly dissociated acids with high H+ release into a weaker acid (König, 1987). Saliva also provides a favorable environment for microorganisms. A drop of saliva contains about 10 million microorganisms, mainly streptococci. Certain strains of streptococci, such as Streptococcus mutans (S. mutans), are the main cause of caries. The presence of mutans streptococci in plaque correlates with the number of streptococci in saliva (Mundorff et al., 1990). When high levels of microorganisms are found in saliva, high levels of bacteria are also found in plaque (Kneist, 1998).

The secreted part of the salivary gland is the acinus. Saliva secretion occurs under the influence of the autonomic nervous system. With parasympathetic stimulation of the glands, more electrolytes and more fluid are secreted, whereas with sympathetic stimulation, protein secretion predominates (Smith, 1996). In general, parasympathetic innervation predominates (Whelton, 1996). The macromolecules of saliva, such as polypeptides and proteins, are synthesized and secreted in the acinar cells of the glands (Smith, 1996). The electrolytes and small organic molecules are derived from the blood plasma, so the primary saliva produced in the glands is isotonic to the blood. Ions (including Na+, Cl-, bicarbonate) are then reabsorbed during the secretion process. This results in saliva that is hypotonic when it reaches the mouth. This reabsorption occurs mainly in the salivary duct (Smith, 1996).

6.1.3.2. The Function of Saliva

The consequences of xerostomia, meaning reduced or absent saliva production, are a perfect example of the important protective function of saliva (Stößer, 1993; Zimmer, 2000). When the dentition of affected patients is examined, it is usually severely damaged by caries (Klimek et al., 1999; Leander Lumikari et al., 2000; Oeschger, 2006).

The function of saliva is as diverse as its composition. In addition to the antibacterial activity of antibodies, lysozyme, lactoferrin and lactoperoxidase, and starch metabolism by amylase and proteases, there are other functions of saliva (Zimmer, 2000).

During a waking state, approximately 20 ml of saliva is produced per hour, with a flow rate for unstimulated resting saliva of approximately 0.25-0.35 ml/min (Nikiforuk, 1985; Puy, 2006). however, when stimulation occurs, such as chewing activity, the value increases to 1-3 ml/min (Nikiforuk, 1985; Tacha, 1999). This mechanism is of great benefit as the increased secretion rate also leads to an improved rinsing function of the saliva, which is particularly beneficial after mealtimes. Food residues, bacteria, desquamated epithelial cells, leucocytes, etc. are washed away with the oral fluid, swallowed into the gastrointestinal tract and excreted from there (Humphrey et al., 2001; König, 1987). The presence of mucins and glycoproteins in saliva gives it a slightly viscous consistency, which helps it to cover and protect the tooth surface and oral mucosa (Van Nieuw Amerongen et al., 2004).

At rest, the pH of saliva is between 6.5 and 6.9 (Baumeister, 2005; Rozeik et al., 1961). In the event of an acid attack, the pH in plaque falls to a critical level of 5.2-5.7 (Oeschger, 2006). Saliva directed towards the acidic side promotes caries predisposition (Rozeik et al., 1961). Stimulation increases the production of sodium and bicarbonate in the parotid and submandibular glands. The presence of buffering systems leads to an increase in salivary pH to 7.0-7.5 (Buddecke, 1981; Humphrey et al., 2001). This buffering capacity allows saliva to neutralize acids from food intake or microbial metabolism, providing important protection (Edgar,1992; Leander-Lumikari et al., 2000). Phosphate and bicarbonate buffers are key systems in oral fluid (König, 1971). The phosphate buffer plays a minor role during acid attack, whereas the bicarbonate buffer is crucial for protecting tooth structure from acid attack (Humphrey et al., 2001; Sheiham, 2001; Van Nieuw Amerongen et al., 2004) as bicarbonate can diffuse through plaque and neutralize acid acting on tooth (Buddecke, 1981; Humphrey et al., 2001)

Saliva also plays an important role in the remineralization of demineralized tooth structure, which will be discussed in more detail in the following section 6.5. (Baumeister, 2005). In addition, saliva is essential for maintaining oral health, but also serves as an important nutrient source for oral microorganisms (König, 1987; Oeschger, 2006). Although the exact influence of saliva on caries formation is not known, a correlation between buffering capacity and caries is accepted (Ericsson, 1959; Shannon et al., 1973; Krasse, 1986).

6.1.3.3. The Flow Rate

The flow rate of saliva undergoes significant fluctuations, and both the composition of total saliva and its pH value and buffering capacity depend on the flow rate, type of stimulation, and duration of stimulation. Changes can be induced by factors such as food intake, smoking (Parvinen 1984), time of day (Ericsson, 1959; Naujoks et al., 1961; Whelton, 1996) or season (Shannon, 1966; Whelton, 1996). Lighting conditions also affect salivary flow, for example, closing the eyes reduces salivary flow, as does being in a darkened room. (Dong et al., 1995). The amount of saliva is also influenced by water intake through drinking (Ericsson, 1959). Chronic malnutrition can affect and reduce both the flow rate of stimulated saliva and its buffering capacity (Johansson et al.; 1992). While age does not affect salivary secretion, reduced flow rates are common in older people, often due to medication. (Heintze et al.,1983; Meurman et al., 1994, Sreebny, 1996). This is because certain drugs have inhibitory effects on salivary secretion. These drugs include antidepressants, diuretics, anticholinergics, sedatives, neuroleptics or antihistamines (Krasse, 1986; König, 1987; Meurman et al., 1994).

Salivary flow is a natural defence mechanism against oral microorganisms and their metabolic by-products by rinsing them out of the mouth and swallowing them. Therefore, flow rate is also an important measure of the removal of harmful substances from the oral flora. Low flow rates have been shown to increase the number of mutans streptococci and lactobacilli in saliva (Krasse, 1986), which play a significant role in the development of caries. Therefore, the flow rate of resting saliva has an important influence on caries activity due to the continuous removal of cariogenic substances (Dawes, 1983).

6.1.3.4. The Buffer Capacity and pH Value

A buffer is a mixture of substances whose pH changes much less when an acid or base is added than the pH of an unbuffered system. It has the ability to keep the pH of a solution relatively constant despite the addition of acids or bases. The buffering effect is based on the conversion of the oxonium ions (H3O+) or hydroxide ions (OH-) introduced by the acid or base into weak acids or bases, which themselves contribute only slightly to the formation of H3O+ or OH- ions. This is especially important in physiological solutions.

An acidic buffer system consists of a weak acid and its conjugated base. The pH of the whole system is determined by the concentration ratio of these two substances. The buffer substance binds hydrogen ions from highly dissociated acids, converting them into less dissociated acids. As a result, the pH of

the solution is unlikely to decrease even when significant amounts of acid are added. Every buffer system has a specific pK value. The optimum buffering effect of the system is in the range of pK ± 1, so the ability of the buffer system to compensate for pH changes is greatest in this range (Löffler et al., 1990). Buffer capacity is the quantitative ability of a system to compensate for pH changes. It is determined chemically by the number (mmol) of protons or hydroxyl ions that cause a pH change of 1.0 in one liter of buffer solution. The unit of measurement is mmol/l/pH. Buffer capacity depends on the total concentration of the buffer system and the distance between the pK of the buffer system and the pH of the solution. It is highest when the pH of the solution to be buffered is equal to the pK of the buffer (Löffler et al., 1990).

The determination of saliva buffer capacity is simplified by many experimenters. The saliva sample is mixed with a weak acid and the resulting decrease in pH is used as a measure of buffering capacity. Although this method deviates from the exact chemical determination of buffer capacity, the simplification is useful because the focus is on the saliva's response to acid attacks from food or metabolic products of oral microorganisms in terms of dental health. This simple approach captures all the different buffering systems in saliva. Such a determination of buffer capacity is a practical method and can be carried out quickly, even with a large number of samples.

Biological solutions such as saliva and blood contain more than one buffering system. In saliva in particular, large pH fluctuations due to food intake must be balanced, so the buffering systems must be able to temporarily cover the pH range of 4 to 9. The ability to neutralize acids serves to protect the teeth from demineralization, as pathological demineralization or erosion of the enamel is expected to occur when the pH falls below 5.7, especially when other unfavorable factors are present. These factors include the duration of acid exposure, the degree of saturation of saliva and plaque with calcium phosphate, the nature and activity of these ions, and the diffusion conditions at the tooth (König, 1987).
It is concluded that the most important buffering range is in the slightly acidic environment with pH values of 5 to 7, where bicarbonate, phosphate and proteins are the main buffering agents. Other substances can also act as buffers. Nitrogenous compounds such as urea, ammonia or basic amino acids (e.g. arginine, histidine, lysine) contribute to the buffering capacity of saliva by acting as weak bases (König, 1987, Rosenhek et al., 1993). Even acetate, the salt of acetic acid, acts as a buffer against the stronger lactic acid produced during sugar glycolysis by accepting protons. The newly formed acetic acid is weaker than lactic acid, reducing further pH drop and limiting tooth demineralization (Margolis et al.; 1985).

Buffer capacity appears to be closely related to salivary flow rate and bicarbonate concentration. For example, smoking has a negative effect on buffering capacity, as does a systemic protein deficiency such as may occur in conditions such as anorexia nervosa (Wikner et al., 1994). Of all the salivary parameters, buffer capacity shows the highest correlation with caries activity (Ericsson, 1959; Krasse, 1986).

6.2. The Microflora as a Factor

6.2.1. Microorganisms in the Oral Cavity

Microorganisms such as bacteria, fungi and viruses are present in the oral cavity (Marsh et al., 2002). The physical contact with newborns by the mother or close persons and food can serve as transmission routes for microorganisms (Behrendt et al., 2002). The oral cavity has both a resident and a transient flora. More than 300 different species of bacteria are part of the oral ecosystem (Eickholz, 1996; Schiffner, 1997). A fungus of great interest is Candida albicans, which is found in the oral cavity of 30 to 50% of the population (Wetzel et al., 1997). Herpes simplex virus, which is common in the oral cavity and can cause a blistering rash, is one of the most commonly isolated viruses in the oral cavity (Marsh et al., 2002). While fungi and viruses are minimally represented in the oral flora, bacteria make up the majority of microorganisms in the oral cavity (Hellwig et al, 1999).

In adults, the average number of microorganisms in "1 ml of saliva" is about 100 million to 1 billion (Pilz, 1980). The biofilms on the back of the tongue are similar to those on tooth surfaces (Baumeister, 2005). Most microorganisms live in symbiosis with their host. They feed on their host's excretions and produce antibacterial substances, enzymes or vitamins from their metabolic products. However, there are also parasitic microorganisms that are dependent on their host and can harm it (König, 1971).

Bacteria have a cellular structure. The outer layer consists of a capsule called the cell wall, which can vary in thickness, and a cytoplasmic membrane. Inside the bacterium is the nucleoid, surrounded by the cytoplasm, where the metabolism of the bacterium takes place (Höf et al., 2005). The cell wall of the bacterium determines its shape, which can be round, rod-shaped or spiral. Round-shaped bacteria are called cocci, rod-shaped bacteria are called bacilli and spiral-shaped bacteria are called spirochetes (Höf et al., 2005). Variations in the structure of the cell wall allow further differentiation. The method developed by GRAM in 1884 makes it possible to distinguish between gram-positive and gram-negative species. Bacteria are stained with a crystal violet iodine complex and then decolorized with alcohol. Species that release the dye (gram-negative) have thinner cell walls, while those that do not (gram-positive) have thicker cell wall (Buselmaier, 2007). Bacteria can be

distinguished not only by their morphology but also by their metabolism. While the use of oxygen for metabolism is essential for some species (aerobes), there are species that cannot survive in the presence of oxygen (anaerobes) (Bowden et al., 1998). There are also bacteria that have the ability to switch their metabolism to adapt to oxygen-poor or oxygen-rich environments. Aerobes and anaerobes that have this ability to switch their metabolism to aerobic or anaerobic pathways are called facultative aerobes/anaerobes (Höf et al., 2005).

In the oral cavity, bacteria can cause caries in addition to diseases of the periodontium. Bacterial metabolism (Featherstone, 2004; Selwitz et al., 2007) is crucial to the development of caries as bacteria produce organic acids as by-products of the breakdown of low molecular weight carbohydrates. It should be noted that it is still not completely clear which bacteria are primarily responsible for the different forms of caries (Zimmer, 2000). For bacteria to survive in the oral cavity, attachment to the tooth surface and mucous membranes is essential, otherwise they would be removed from the oral cavity by saliva when swallowed. Over time, plaque forms, which, along with host and dietary factors, is another criterion for developing caries (Marsh et al., 2002).

6.2.2. Intrinsic Versus Extrinsic Acid Erosion

When considering chemical demineralization of the tooth, both intrinsic and extrinsic sources of acid should be taken into account, as in addition to caries caused by bacteria, chemical demineralization of the tooth can also occur without bacterial influence, known as erosion (Schroeder, 1991). Acid-induced tooth damage can occur in a number of ways. Erosion and caries are two such forms of acid-induced damage. While caries is caused by acids produced by bacteria in the mouth as they process sugars and carbohydrates and secrete acids that attack the tooth enamel, leaving holes in the enamel that, if left untreated, can lead to dental caries, erosion is described as a chemical demineralization of the tooth without bacterial influence.

Intrinsic erosion of teeth is caused by psychosomatic and somatic conditions such as bulimia nervosa. Teeth are destroyed by intrinsic acid, i.e. stomach acid (Ommerborn et al., 2005). In bulimia patients, the regular contact of the teeth with stomach acid due to vomiting can lead to severe damage to the tooth enamel, especially on the inside of the upper front teeth (Koch, 1999). Repeated exposure of the tooth enamel to stomach acid can lead to rapid erosion of the enamel, resulting in sensitive teeth, tooth decay and other dental problems.

Extrinsic erosion is the loss of tooth enamel due to acids that come from outside the body (Ommerborn et al. 2005) such as from the consumption of juices and cola (Schroeder, 1991;

Prophylaxe impuls, 2005) or ascorbic acid, vinegar and citrus fruits (Koch, 1999). This also includes baby bottle tooth decay, which is caused by the continuous consumption of mostly sugar-sweetened teas or juices. These acids can attack the tooth enamel and cause erosion, which can show up as shiny, smooth spots on the teeth.

6.2.3. Formation of Plaque

The main cause of dental caries and periodontal disease is the formation of microbial plaque (Wiedemann, 1993) , which develops in various stages. Dental plaque is a complex community of microorganisms that forms on the surface of teeth and contributes to human immune defense. However, when plaque reaches a certain thickness and the microbial composition changes, it can make the host tooth susceptible to disease (Marsh et al., 2002).

An established plaque consists of densely packed bacteria embedded in an amorphous substance called the plaque matrix. Approximately 60-70% of the total plaque is made up of bacterial cells, while the matrix is made up of proteins, lipids, extracellular polysaccharides and salivary substances. The remainder is made up of sulcular fluid, which helps to maintain structural integrity (Silverman et al., 1967). The inorganic component of plaque makes up only 5-10% of its dry weight, but has a higher concentration of calcium and phosphate than saliva (Dawes et al., 1962). Small amounts of potassium, sodium, magnesium, copper, zinc, lead, iron, strontium and fluoride are also present. Calcium is present in non-ionized form and may play an important role in enamel remineralization in the event of a pH drop. The concentration of fluoride in plaque is 5-10 ppm, mainly present on or within bacteria in the form of calcium fluoride or fluorapatite. Studies have shown that when the pH drops due to carious attack, a decrease in fluoride and other minerals occurs (Agus et al., 1980). Individuals with lower levels of caries have been found to have higher concentrations of calcium, phosphorus and fluoride in plaque. The presence of these minerals in plaque plays a role in cariostasis and in the remineralization of incipient lesions (Agus et al., 1980; Ashley, 1975).

6.2.3.1. Classification of Plaque

Plaque is divided into supragingival and subgingival plaque depending on its location. Supragingival plaque is mainly found in interdental spaces, fissures, cervical thirds of crowns and root furcations. Because of the different conditions on the tooth, the composition of plaque varies; different surfaces provide different nutrients and require different shear forces to remove. In contrast, subgingival plaque is thin and sparse on healthy teeth, whereas pathological processes can lead to larger bacterial accumulations in gingival pockets (H. Schroeder et al., 1970). Fissure plaque also differs from plaque

on the smooth surface of teeth because fissures serve as preferred sites for food debris and can make oral hygiene more difficult, facilitating the colonization of even less adhesive bacteria. This means that the microbial composition of plaques from different sites in the oral environment, and even from different surfaces of the same tooth, are unique (Donoghue, 1974).

6.2.3.2. Spectrum of Plaque Bacteria

After a tooth has been cleaned, a thin acellular film consisting of lipids, sulcus fluid, and saliva proteins such as glycoproteins, phosphoproteins, serum proteins, enzymes, and immunoglobulins forms on the tooth surface within minutes (Steinle, 2003) or even seconds (Zimmer, 2000; Hannig et al., 2005). This layer, which has a thickness of about 0.01-1 µm (Steinle, 2003) is also referred to as acquired or secondary enamel pellicle (Lendenmann et al., 2000). The negatively charged saliva proteins, which make up the majority of the pellicle, can bind to the calcium and phosphate groups of the apatite in the tooth hard substance through electromagnetic forces (Steinle, 2003). The semipermeable nature of the secondary enamel pellicle allows for limited regulation of the exchange process between the oral cavity, plaque, and tooth. Furthermore, it provides some protection against abrasion by keeping the tooth moist (Hannig et al. 2006; Lendenmann et al., 2000).

Within a few hours after tooth cleaning, the acquired pellicle is colonized by so-called pioneer species, which are cocci-shaped bacteria. They belong to the Neisseria and Streptococcus species. Among the first colonizers of the pellicle are bacteria of the species S. sanguis (Rosan et al., 2000), followed by S. oralis, S. mitis, A. viscosus and Veillonella in the early stages of plaque development (Socransky et al., 1977; Marsh et al., 2002). These pioneer organisms attach to the secondary enamel pellicle by adhesion and cohesion forces, such as van der Waals forces and electrostatic forces (Folwaczny et al.m 2003). In addition, there are components on the cell surface of microorganisms, specific binding molecules called adhesins, which are able to bind to receptors of the pellicle proteins (Hannig et al., 2007; Schroeder, 1991; Zimmer, 2000).

The bacterial population attached to the secondary enamel pellicle begins to proliferate and colonize (Marsh et al., 2002) a matrix of sticky extracellular polysaccharides, other polymers and additional saliva proteins (Sutherland, 2001). The result is a confluent growth known as a biofilm Marsh et al., 2002), which continues to grow through cell division and the attachment of more bacteria from saliva (Folwaczny et al., 2003; Listgarten, 1994). Pioneer species use their metabolism to create suitable conditions for more demanding bacterial species. This stage leads to an increasing diversity of plaque microflora. The oxygen initially present in the plaque is consumed by aerobic species and replaced

by carbon dioxide or other gases, which are by-products of bacterial metabolism and promote the growth of anaerobic bacterial species (Marsh et al., 2002; Marsh, 2003). While the plaque is still dominated by streptococci after seven days, this dominance shifts in favor of anaerobic rods and filaments after about fourteen days (Kolenbrander et al., 2006).

With progressive plaque accumulation, the once aerobic/facultative aerobic bacterial flora changes with an increasing proportion of filaments and anaerobic rods, which quantitatively dominate after seven to fourteen days. As the plaque ages, the proportion of anaerobes increases, as evidenced by the decreasing redox potential (-100mV to -300mV) of the plaque (Ritz, 1967; Kenney et al., 1969). While plaque growth is limited by antimicrobial substances in saliva, oral hygiene and the shear forces of mastication, these growth inhibiting mechanisms are partially offset by reattachment of microorganisms (Folwaczny et al., 2003). An established plaque consists of densely packed bacteria that make up 60-70% by volume and are embedded in the plaque matrix. The removal of plaque by the self-cleansing forces of the oral cavity (such as saliva flow) is no longer possible in this state (Schroeder, 1997).

6.2.3.3. Plaque as a Microbial System

Bacteria can detach from an existing biofilm and colonize a new location. Using a variety of adhesion and co-adhesion mechanisms and physicochemical interactions, they can create a complex, physically and functionally structured biofilm. The resulting interactions can be synergistic or antagonistic in nature, depending on the benefit to the individual cultures involved.

In addition to its bactericidal properties, saliva serves as the main nutrient source for microorganisms (Lehmann et al., 2005). It also delivers salivary proteins to the tooth surface for bacteria to adhere to. Metabolism in plaque creates different gradients of nutrient availability, pH, oxygen and toxic/growth inhibitory by-products. This allows the coexistence of bacteria with different requirements that would not survive in a homogeneous culture. To meet their nutritional needs, microorganisms must cooperate. In a cooperative relationship there is a stepwise breakdown of complex molecules involving different bacteria with different enzymatic capabilities (synergistic interaction) (Marsh et al., 2002). Typically, they have overlapping activity patterns for proteases and glycosidases that interlock during catabolism. Bacteria that act as primary consumers and provide their metabolic end products to other organisms being secondary consumer, as a primary nutrient source are another example of synergistic nutrient use. Microorganisms can also inhibit or prevent the presence of foreign or competing bacterial strains by producing bacteriocins. The densely packed attachment of

microorganisms also protects against the colonization of exogenous microorganisms, known as antagonistic interaction. The balance of synergistic and antagonistic interactions provides plaque stability that can be largely maintained despite external influences such as the host immune response (Marsh et al., 2002; Marsh, 2003).

Irrespective of any endogenous influences, environmental stimuli or microbial diversity in the plaque, there is a certain stability and dynamic equilibrium between the different bacteria and their environment, termed microbial homeostasis (Marsh et al., 2002).

In principle, the presence of plaque does not necessarily imply pathogenic processes unless there is a disturbance in homeostasis. This phenomenon is often observed with frequent intake of easily fermentable mono- and disaccharides and the associated acid production by some bacteria (Cury et al., 2000). If the pH in the plaque decreases significantly, the metabolic rate of individual bacteria decreases or ceases. This is beneficial to the pathogenic plaque bacteria, which are able to maintain their metabolic activity under acidic conditions and can therefore multiply unhindered in the plaque. The main cariogenic bacteria are S. mutans and lactobacilli (Klimek et al., 1999; Marsh, 2003).

6.2.4. Caries as a Microbial Infection

Although many factors play a role in the development of caries, it is undisputed that the lesions are the result of bacterial interaction.

Streptococcus mutans, lactobacilli, and their special significance in the formation of caries

Streptococcus mutans is the main pathogen in the etiology of enamel caries in children and adults, root caries in older adults and smooth surface caries in infants, as has been demonstrated by epidemiological studies (Marsh et al., 2002; Marsh, 2003) and confirmed by animal experiments. These studies have shown a correlation between the occurrence of caries and the presence of S. mutans (Rupf et al., 2007; Weidenauer, 2001). Patients with a high prevalence of caries show a higher colonization of tooth surfaces with S. mutans than patients with a lower prevalence. Carious lesions also have a higher colonization density of S. mutans than caries-free tooth surfaces. This confirms that caries is usually preceded by S. mutans colonization and highlights the important role of the bacterium in caries formation (Klimek et al., 1999; Wetzel et al., 1997).

The S. mutans species of gram-positive cocci is one of the four main types of oral streptococci.

S. mutans bacteria are gram-positive, facultative anaerobic cocci that are classified into Streptococcus mutans groups based on their morphology. The second most commonly isolated species is S. sobrinus, which also plays a - slightly unclear - role in caries, as many studies did not distinguish between S. sobrinus and S. mutans. In addition to S. sobrinus, S. cricetus and S. rattus are also important in caries formation, as they can occur in different combinations with S. mutans. The most commonly isolated species of the mutans group in humans are S. sobrinus and S. mutans, and the rarer S. cricetus (Marsh et al., 2002).

The special role of bacteria in caries formation is explained by their ability: Firstly, they can form organic acids in the presence of low-molecular-weight carbohydrates, and secondly, they can synthesize extracellular polysaccharides that allow the bacteria to adhere firmly to the tooth surface (Sutherland, 2001). In addition, they promote the formation of a highly cariogenic plaque by providing numerous receptor binding sites for microorganisms, facilitating the networking and proliferation of the plaque (Hamada et al., 1980, Banas, 2004). In addition, some species of the mutans group are capable of forming intracellular polysaccharides that serve as carbohydrate stores and are converted to acid when carbohydrates are no longer provided by the diet (Spatafora et al., 1999).

An additional characteristic of S. mutans is its acid tolerance, as the bacterium has the ability to survive in acidic conditions (pH < 5) where other acid-producing bacteria cannot exist (Svensaeter et al., 1997). In fact, the number and activity of S. mutans increases as the pH decreases (Hamilton et al., 1991; Harper et al., 1984). This is due to the bacterium's ability to pump acid out of its cells against a concentration gradient, allowing it to maintain its metabolism in acidic conditions and continue to produce acid (Belli et al., 1991; Hamilton et al., 1991).

This is a characteristic that it shares with lactobacilli. Lactobacilli are gram-positive, facultative anaerobic rods that contribute to the progression of caries in an existing initial carious lesion due to their high acid tolerance. These highly acid-producing organisms are responsible for the progression of caries rather than the formation of caries (Balakrishnan et al., 2000; Marsh et al., 2002). Lactobacilli typically make up less than 1% of total cultivable microflora of the oral cavity (Marsh et al., 2002). Their numbers increase when S. mutans colonizes the oral cavity and creates a favorable acidic environment for lactobacilli (Newburn, 1992).

Lactobacilli have a preference for acidic environments and have been shown to be more resistant to antimicrobial agents such as chlorhexidine or fluoride than S. mutans (Breighton et al., 1998). Since

lactobacilli, unlike S. mutans, are unable to bind independently to tooth surfaces, they require retentive areas with low pH and areas of plaque accumulation (Breighton et al., 1998). Advanced carious lesions may provide such a habitat for lactobacilli. The presence of carious lesions correlates with the number of lactobacilli in both children and adults (Byun et al., 2004; Chhour et al., 2005). Lactobacilli are also considered an indicator of open carious lesions. The number of lactobacilli correlates with the frequency and amount of carbohydrate intake (Marsh et al., 2002). Therefore, a high caries risk is not only determined by the presence of S. mutans but also by the presence of lactobacilli. Assessing the presence of both types of bacteria is advantageous for estimating caries risk (Loesche, 1986).

6.2.5. Acid Production and Acid Attack

The consumption of sweets and sugary drinks introduces sugar into plaque, where it is metabolized into energy. This is done by breaking down sucrose into pyruvic acid and finally lactic acid through glycolysis. Over 90% of the metabolic end products of streptococci and lactobacilli are lactic acid. This rapidly lowers the pH of the plaque to a critical range between 4.2 and 5.7, promoting demineralization of the enamel. Once the fermentable substrates have been removed by saliva, preventing further carbohydrate metabolism, the metabolic process stops and the body's buffering systems intervene to slow the decline and stabilize the pH.

The time from the first drop in pH to the return to neutral is called "oral sugar clearance" and typically takes 30 minutes. This process can be graphically represented by the Stephan curve. When the pH rises above a critical level, minerals can be deposited in plaque. This can promote both the remineralization of damaged enamel and the formation of tartar (Meyer-Lückel et al., 2012). The strength of the acid attack depends, among other factors, on the carbohydrate supply, with the most significant pH reduction expected from mono- and disaccharides. Sucrose is transported and metabolized more efficiently than glucose, raffinose or lactose (Martin et al., 1979). In addition, it has been observed that low fluoride concentrations can inhibit intracellular sugar transport and reduce the rate of metabolism. In contrast, acid production is limited with unrefined or refined starch, as the buffer capacity is not fully used. This is because acid can only be produced by the prior catabolism of maltose by bacterial amylases. The slow diffusion of starch into bacteria due to its molecular size could be a possible explanation.

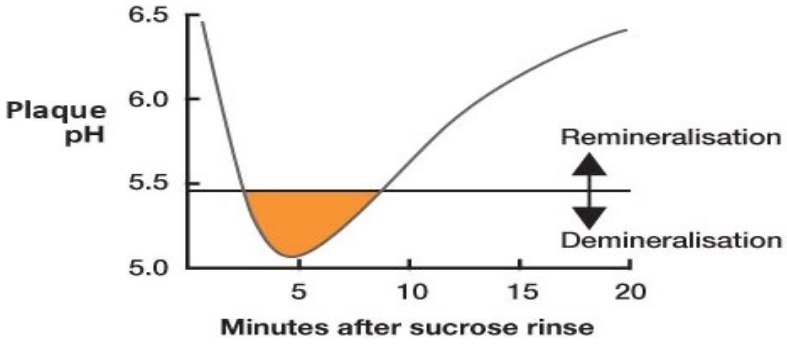


Fig. 7 Stephan Curve (Garland Polly, 2024)

6.3. The Substrate as a Factor

6.3.1. Impact of Nutrition on Dental Caries

Throughout human evolution, both the quality of food and eating habits have changed and will continue to change. Dietary factors play a role in the development of dental caries in two ways. Firstly, food has a systemic effect and secondly a local effect on the teeth. However, the systemic effect is only relevant during tooth development (König, 2000).

Associations have been found between deficiencies in vitamin D, calcitonin and parathyroid hormone, which affect the regulation of calcium and phosphate levels in the body, and hypocalcemia and the development of enamel hypoplasia, irregularities in the structure of the hard tooth tissue, resulting from malnutrition during tooth germ development (Klimek et al., 1999; Psoter et al., 2005; Nikiforuk et al., 1997). However, a defective or irregularly mineralized tooth hard tissue does not necessarily mean a higher caries risk for the affected patient compared to a properly developed tooth (König, 2000).
Rather, the effects of malnutrition on caries prevalence are shown indirectly, for example through protein deficiency, which can affect salivary flow and therefore oral health (Williams et a., 1982).

Similarly, the effect of the physical properties of the diet on cariogenicity has not been extensively studied. From a dental perspective, any food that has a longer residence time and lower solubility will require prolonged oral clearance and increased oral hygiene. In contrast, plant foods are high in fiber and cellulose, which provide mechanical cleaning of tooth surfaces. Therefore, the consumption of raw fruit and vegetables is already a well-established aid to oral hygiene (Klimek et al., 1999).

The chemical composition of food may also be important, as it is known to influence salivary flow rate. Stimulated saliva is more alkaline and supersaturated with calcium and phosphates, which could

have a caries-inhibiting effect. The concept of caries-protective factors of natural products has also been demonstrated, as experimental evidence showed faster and greater enamel dissolution in a solution of saliva with refined products compared to a mixture containing bran, wheat germ and sugar cane juice. It is not only the acid production of bacteria that can damage tooth enamel, but also excessive consumption of acidic foods, such as fruit acids in fruits like apples and lemons, fruit juices and carbonated drinks, as prolonged contact with tooth enamel leads to demineralization (Klimek et al., 1999; Psoter et al., 2005; Nikiforuk et al., 1997).

6.3.2. Significance of Sucrose for the Etiology of Caries

More important for the development of dental caries is the local influence of food, which is not limited to a specific period of development, but has a constant effect on the teeth. The focus is on easily fermentable mono- and disaccharides and, to a lesser extent, starch (Burt et al., 2001; König, 2000).

Of all the dietary changes in the last century, the qualitative and quantitative changes in carbohydrate consumption have been the most significant. The consumption of starch products has decreased, while the consumption of refined sugars has increased (from one third in 1900 to one half today). Carbohydrates now represent 50% of the calories consumed each day (Page et al., 1974).

Since the Vipeholm study, it has been known that there is no direct proportionality between the sucrose concentration in food and its cariogenicity, but that the frequency of sugar consumption, intra-oral retention time and oral clearance are essential factors. The effective concentration of sugar is as important as the frequency of consumption (Gustafsson et al., 1954).

Microorganisms in the oral cavity can absorb low molecular weight sugars, metabolize them glycolytically and convert them to acids. These acids can attack tooth enamel and, if exposed for long enough, lead to initial caries (König, 1992; Sheiham, 2001). For example, many monosaccharides are metabolized by bacteria for energy (ATP synthesis), producing corresponding acids as by-products that can attack enamel. In addition to being the most commonly used sugar in industrialized countries, sucrose plays an important role for several reasons (Borutta et al., 2005; Sheiham, 2001). Because sucrose is highly soluble, it can easily diffuse into plaque. Bacteria break down sucrose into two monosaccharides, fructose and galactose, which are then metabolized into monosaccharide-like acids. The uniqueness of sucrose is that the cleavage of the glycosidic bond releases energy that is used to synthesize soluble and insoluble extracellular polysaccharides. These polysaccharides aid adhesion, particularly of S. mutans, and serve as reserves to enable the bacterium to survive for a period of time

when substrate availability is low (Marsh et al., 2002). Unlike other disaccharides such as maltose or lactose, sucrose can act directly as a glycosyl donor in polysaccharide synthesis, and the high energy released during sucrose hydrolysis allows the synthesis reaction to proceed without further energy input. In conclusion, all common sugars are cariogenic, but sucrose plays a special role in the etiology of caries due to its properties and frequent consumption.

Because of their adhesive properties, the extracellular water-insoluble polysaccharides formed by enzymatic cleavage in plaque prevent saliva from reaching the tooth surface. This prevents saliva buffering enamel, which is highly susceptible to acid attack (Steinberg et al., 1999). In addition, these complex sugars allow additional adhesion of plaque bacteria to the tooth surface, promoting the growth of highly cariogenic plaque (Banas, 2004; Kuramitsu 1993). In combination, extracellular polysaccharides can serve as a nutrient source for plaque bacteria (Sutherland, 1999). Starch, a complex sugar made up of glucose, is the basic substance of plants consumed by humans in the form of vegetables, fruit and bread. However, the consumption of starch is associated with a lower risk of tooth caries than the consumption of sugar or starch in combination with sugar. This is due to the slow breakdown of unrefined starch by salivary amylase. In addition, the resulting polysaccharide molecule is too large to diffuse into plaque (Lingström et al., 2000; Selwitz et al., 2007; Sheiham, 2001).

Based on this fact, König presents his hypothesis of "low caries prevalence in developing countries", attributing it to the absence of sugar and the frequent consumption of starchy foods. In conclusion, sugar-free starch products are clinically much less cariogenic than foods containing sucrose (König, 1992).

6.4. The Time as Factor

Plaque bacteria not only need a place to attach, but they also need to be there for a long time in order to produce acids after substrate uptake, which then have to act on the tooth surface for a long enough time to cause demineralization (Fejerskov, 2004). Consequently, a carious lesion can only occur if the subsequent acid attacks are not constantly neutralized by saliva (Featherstone, 2004).

6.5. De- and Remineralization on the Tooth Surface

The apatite crystals of tooth enamel consist mainly of calcium and phosphate ions, and saliva is also a calcium and phosphate saturated solution (Featherstone, 2000). At a physiological saliva pH of 6.5-6.9, there is a dynamic equilibrium between the ions of tooth enamel and saliva (Knappwost, 1952). When plaque forms on the tooth surface and sugar is regularly consumed, the balance between the tooth surface and saliva can be disturbed (Featherstone, 2006). The cariogenic microorganisms in the plaque produce organic acids from the dietary sugars consumed, causing the pH in the plaque to decrease to the critical range of 5.2-5.7, and a small proportion of the acids diffuse into the enamel (Featherstone, 2000). This leads to the dissolution of ions from the hydroxyapatite crystals of the tooth surface. This disrupts the equilibrium and creates a concentration gradient between the enamel and the saliva. As a result, organic acids continue to diffuse into the enamel, using the hydration layer around the crystals as a diffusion pathway. The acids attack the apatite crystals in the enamel, causing ions to diffuse into saliva. This process is known as enamel demineralization (Hellwig et al., 2006).

Demineralization continues as long as sufficient acid is produced by microorganisms (Balakrishnan et al., 2000). However, as the pH increases, the balance shifts in the opposite direction. This results in compensation for mineral loss by rediffusion of ions from the saliva into the enamel. These ions can either form new crystals or be deposited on the surface of already damaged crystals. This process is called remineralization (Haibel et al., 2005; Kidd et al., 2004; Schroeder, 1997).

As long as demineralization and remineralization are balanced and the pH in the plaque only briefly falls into the critical range, the tooth surface remains clinically unchanged (Featherstone, 2004). However, with prolonged frequent sugar consumption and a disruption in the physiological balance between demineralization and remineralization, chronic mineral loss accumulates into an initial carious lesion (König, 1992; Selwitz et al., 2007).

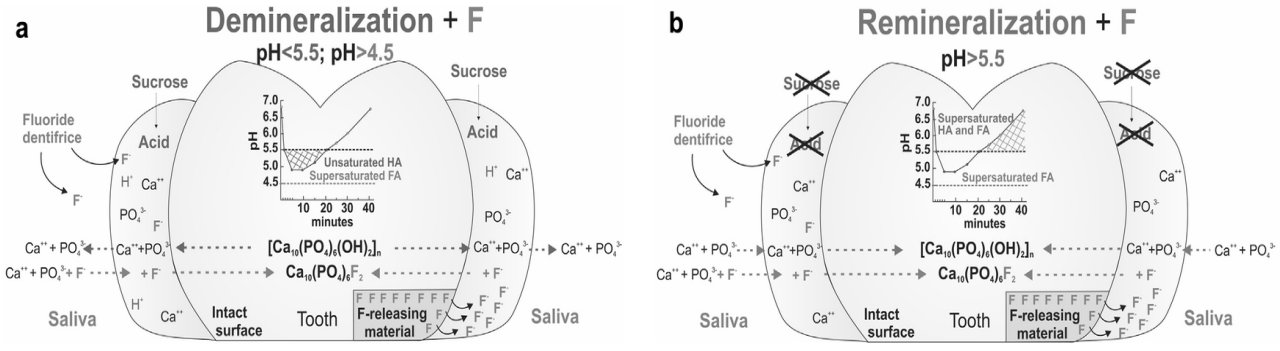


Fig. 8 De- and Remineralization Process on the Tooth Surface (Aparecido Cury et al., 2016)

7.Concept of Prophylaxis in Modern Medicine

The concept of prophylaxis in modern medicine involves a holistic approach to health prevention based on healthy lifestyle guidelines. It includes measures such as education, nutrition and hygiene to promote health and prevent disease. Preventive measures aim to avoid diseases and their outbreak (Hunter, 1995). Early detection aims to identify stages of disease, such as early-stage tooth caries. Rehabilitation and therapy aim to prevent disease progression and restore health. Follow-up care is important to maintain the success of treatment and achieve the goal of stopping the disease (Fejerskov et al., 1998).

Even with almost unlimited economic resources in the health care system, it is not possible today to prevent the onset of tooth caries or periodontal disease a priori because many people do not take the recommended non-invasive measures seriously. In addition, preventive measures are not equally applicable to people from different social and cultural backgrounds (Christianens et al., 2004).

In general, gingivitis, cavities and periodontitis could be prevented and controlled (Van der Sanden at al., 2003). In all cases, their progression can be delayed (Horowitz, 2004).
The aims of dental prophylaxis are:
- to support and accompany the development of the stomatognathic system
- to maintain and promote basic health
- prevent the recurrence of diseases after therapies.

7.1. The Types of Prevention

The objectives are achieved through a variety of measures based on a thorough understanding of the causes and progression of caries. It is important to consider both primary, secondary and tertiary preventive measures to effectively protect and maintain oral health (Hunter, 1995).

Primary prevention, which starts before a child is born and is provided to parents, is essential to ensure long-term oral health. They include education about the importance of good nutrition and proper oral hygiene. Secondary preventive measures include regular dental check-ups and aim to prevent diseases such as caries or gingivitis in general, for example by using fluoride to strengthen tooth enamel or fissure sealants to prevent caries in the pits and fissures (O´Reilly et al., 2013; Benson et al. 2013). Tertiary prevention focuses on treating existing carious lesions before they spread and cause major problems, and limiting the recurrence of dental problems after diagnosis and treatment (Hunter, 1995).

The distinction between basic and individual prophylaxis is also important because it takes into account the needs and risk factors of each individual patient. Basic prophylaxis includes general oral health measures, while individual prophylaxis addresses the specific needs and risks of each patient. By combining different preventive measures, improvement of oral health can be achieved (Van der Sanden at al., 2003).

8.Diagnostic

Given the multiple possibilities of pathogenic risk factors for the development and maintenance of caries, it is not unreasonable to suggest that diagnosis should not be limited to the individual tooth but be extended to the entire patient level (Hellwig et al.,2010; Gängler, et al.,2010). The diagnosis of dental caries is initiated by taking a detailed medical history and gathering information on preventive behaviors such as fluoride use, toothbrushing habits and diet. In children, this information is often provided by parents or caregivers. This is followed by a clinical examination of the oral cavity and teeth to assess oral hygiene and the extent of caries (Schmoeckel et al., 2020; Pitts et al., 2013; Bürklein et al., 2011).

The diagnosis of caries begins with the identification of typical clinical symptoms. Visual or other techniques are then used to detect carious changes in the enamel or dentin. After lesion detection, the stage and activity of the lesions are assessed. Treatment is then adapted as only active lesions require treatment. A distinction is also made between cavitated and non-cavitated lesions. Smaller cavities can be treated with micro-invasive or non-invasive measures, while cavitated lesions and hard-to-reach tooth surfaces may require invasive therapy.

In addition, following light sources and imaging techniques can be used to assist in caries diagnosis (Pitts, 2001), especially in areas that are difficult to see visually, such as the proximal areas between teeth. Radiography, particularly bitewing radiographs, is considered the gold standard for detecting proximal caries. In addition, specialized diagnostic equipment such as Fibre optic transillumination (FOTI) can be used that involves shining light through the tooth to identify carious areas as dark spots. Digital Imaging Fibre Optic Transillumination (DIFOTI) takes this a step further by recording the findings with a built-in digital camera. Another option is the Laser-assisted caries diagnosis that uses laser fluorescence and quantitative light-induced fluorescence (QLF) to differentiate between healthy enamel and carious areas based on their fluorescence under specific wavelengths of light and provide additional information about carious lesions and make a more accurate assessment. The use

of blue-violet light can help distinguish between healthy enamel (green fluorescence) and carious areas (red fluorescence). The bioluminescence method with the Calcivis system utilizes a photoprotein to emit blue light, indicating the presence of free calcium ions in active carious lesions. This allows for the assessment of caries lesion activity. Electrical resistance measurement is another technique used to detect caries, as caries can cause a decrease in a tooth's electrical resistance due to loss of insulation. Various visualization techniques can aid in the efficient and thorough removal of caries during treatment, including Fluorescence Aided Caries Excavation (FACE), caries detection dyes, chemo mechanical caries removal (Carisolv), and conventional removal with rotating carbide burs (rose burs). These diagnostic procedures can help detect caries at an early stage and allow targeted treatment to maintain dental health (Meyer-Lückel et al.,2012; Gängler et al.,2010; Hellwig et al., 2010).

9.Treatment

The aim of invasive caries treatment is to remove the carious tooth substance without affecting healthy tooth structures. For a long time, the criteria for the extent to which caries should be removed from a cavity and the point at which it should be removed were imprecise and subjective. Traditionally, caries is removed non-selectively, but there is then a risk of pulp damage and subsequent loss of other tooth structures during endodontic treatment (Rickets et al., 2013). An optional method for treating caries in two stages is the stepwise removal of caries. Firstly, carious dentin close to the pulp is left in place and the cavity is provisionally sealed. This is followed by remineralization of the areas near the lesion through the formation of tertiary dentin. After 3-6 months, the cavity is reopened to remove the remaining carious dentin and finalize the treatment (Bjorndal et al., 1997). Studies have shown that the remaining, probably still infected dentin becomes harder and drier during the stepwise caries removal due to remineralization processes, while the number and pathogenicity of the microflora decreases (Bjorndal, et al., 2000). It is therefore necessary to consider whether a second access to the cavity is necessary. Selective caries removal eliminates this step. Instead, the carious dentin is left close to the pulp and the defect is immediately sealed with an adhesive (Bjorndal et al., 2010). This reduces the risk of pulp damage. Studies have shown that the risk of pulp vitality damage is lower with selective caries removal than with stepwise caries removal, although the size of the defect also plays a role (Ribeiro et al., 2012).

In addition, there are non-invasive treatment methods that can delay restorative caries therapy. This will be discussed in more detail in the following chapters.

10.Determinants of Caries Prevention

The main goal of dental preservation is to maintain the health of the teeth by taking measures to remove dental plaque and promote motivation for a healthy diet (Geurtsen et al., 2016). Since behavioral patterns, as well as social behavioral problems, educational and learning deficits, are imprinted in early childhood (Wennhall et al., 2008; Yüksel, 2010), preventive measures must start early to avoid health risks with effects into adulthood (Felitti, 2002).

In 1974, Rosenstock developed his Health Belief Model, which states that cognitive factors influence health behavior. People only behave preventively if they subjectively perceive the health risk, the disease negatively affects their life, and the costs of the disease are higher than the costs of preventive measures. Bandura's concept of self-efficacy was integrated into this model, emphasizing that behavior changes are more likely when a person believes they are capable of implementing and maintaining the measures. Education is the basis for behavior changes in the preventive field, even if these changes can occur gradually (Prochaska et al., 1997).

In the previous decades, significant progress has been made in reducing caries through education and behavioral change. However, it remains a challenge to communicate the value of preventive measures, as their positive effects often take a long time to be noticeable. Patience and a long-term perspective are required to fully understand and implement the importance of oral preventive measures. (Geurtsen et al., 2016; Gülzow et al., 1987; Krüger et al., 1987; Helfenstein et al., 1991).

The basics of oral prevention are based on three pillars that aim to minimize the four main factors of caries formation. These pillars include measures to reduce plaque (oral hygiene), fluoridation and a balanced diet. These three pillars of caries prevention are also supported by the use of fissure sealants. In order for prophylactic measures to be effective, it is necessary to educate individuals about oral health behaviors and, as a result, their compliance in applying what they have learned in their daily lives. Access to professional dental care must also be ensured (Geurtsen et al., 2016).

10.1. The Oral Hygiene as Determinant

To eliminate the main causes of caries - bacteria and time - it is important to develop an age-appropriate oral hygiene program. Oral hygiene measures aim to prevent and remove plaque. This includes regular tooth cleaning, flossing, mouthwashes and other techniques to maintain oral health and prevent dental caries and gum diseases.

Preventive measures begin with counselling and screening of expectant mothers during pregnancy. Preventing oral disease not only protects the unborn child, but a healthy maternal oral flora also has a positive effect on the newborn. Children born to mothers with actively carious teeth tend to have more cariogenic bacteria and therefore an increased risk of caries (Schiffner, 2016). A caries-prone and neglected maternal dentition is generally considered a risk factor for the development of dental caries (Hellwig et al., 2013).

Regular brushing with fluoride toothpaste is recommended from the eruption of the first milk tooth at around six to eight months of age (Geurtsen et al., 2016). Studies have shown that brushing twice a day is more effective against caries than brushing once a day (Hellwig et al., 2013; Marinho et al., 2003; Borutta et al., 2005). Children have significantly better dental health if they start brushing before the age of one, and parents can support their children's brushing beyond the age of three by supervising and if necessary, brushing their teeth (Yüksel, 2010).

Mechanical Intervention to Reduce Biofilm

Caries is caused by the metabolic activity of a pathogenic bacterial biofilm on teeth. It is therefore logical and biologically plausible that caries can be prevented by appropriate mechanical removal or chemical manipulation of this biofilm. Consistent oral hygiene measures can help achieve this goal, although there is insufficient evidence from clinical trials to prove that caries can be prevented by mechanical oral hygiene measures alone (Davies RM et al., 2003). Regular daily tooth brushing can reduce plaque by an average of 42%. Depending on the plaque index used, the values can vary between 30 and 53% (Slot et al., 2012). There is no clear evidence that such a reduction in plaque always correlates with a reduction in caries risk. However, it is suggested that the caries-inhibiting effect of tooth brushing may depend more on the quality of tooth brushing than on the frequency of tooth brushing (Brothwell et al., 1998). The duration of oral hygiene measures plays an important role. On average, brushing for one minute reduces plaque by 27%, while brushing for two minutes reduces plaque by 41%. However, there is no clear data on the exact duration and frequency of brushing (Attin T et al., 2005). In contrast, regular tooth brushing twice a day with fluoride toothpaste has been shown to be an effective method of preventing dental caries. Brushing several times a day with fluoride toothpaste may even be more effective than brushing once a day (Hellwig et al., 2013; Marinho et al., 2003). Both manual and electric toothbrushes can be used to remove biofilm, although electric toothbrushes with oscillating, rotating or reciprocating movements are thought to be more effective (Sicilia et al., 2002).

The use of aids such as dental floss or interdental brushes is recommended because conventional toothbrushes cannot fully reach the interdental space. Regular use of these aids reduces the risk of proximal caries by helping to remove biofilm and food debris between the teeth where conventional toothbrushes cannot effectively clean (Wright et al., 1979). There is weak, unreliable evidence that the additional use of dental floss/interdental brushes achieves a small reduction in proximal plaque (Sambunjak et al., 2011). However, the combination of thorough mechanical removal of biofilm with a toothbrush and regular use of fluoride appears to overcome the caries-inhibiting effect of dental floss. Nevertheless, the use of aids such as dental floss and interdental brushes is recommended because they can remove plaque better than a toothbrush alone, resulting in a caries-inhibiting effect.

Chemical intervention to Reduce Biofilm

In addition to mechanical aids, chemical plaque control agents such as rinses, gels and varnishes are used to remove oral biofilm and influence the metabolism of cariogenic microorganisms. These products often contain antibacterial agents such as chlorhexidine, cetylpyridinium chloride or fluoride, which can help reduce the number of harmful bacteria in the mouth and inhibit plaque formation. Although there is clear evidence that the use of such products leads to a reduction in bacterial levels, data on the caries-reducing effect of these products is very limited and controversial (Bader et al., 2001; Rethman et al., 2011; Van Rijkom et al., 1996). There is evidence that the use of chemical plaque inhibitors in patients already using fluoride supplements for caries prevention does not provide additional caries protection. However, the use of chlorhexidine varnishes has been shown to reduce caries in certain areas, such as fissures in erupting molars and root caries (Slot et al., 2011; Twetman, 2004).

10.2. The Nutritional Guidance as Determinant

There is convincing evidence from animal, epidemiological and experimental studies in humans of a link between sugar consumption and the development of dental caries, an indirect consequence of its metabolism into acids that attack tooth enamel (Scheinin et al., 1976). Both the absolute amount of low molecular weight carbohydrates and the frequency and consistency of sweet foods appear to increase the risk of caries (Geurtsen et al., 2016). The pH cannot be neutralized by frequent snacking and the acidic effect remains.

Until about 1970, a clear correlation between sugar consumption and caries prevalence was observed in many countries (Screebny, 1982). In this context, sugars include all mono- and disaccharides. Free

sugars include all sugars added to foods by manufacturers or consumers, as well as naturally occurring sugars in honey, fruit juices, syrups, etc. Although other fermentable carbohydrates are cariogenic, epidemiological studies have shown that starchy staple foods and fresh fruit are only weakly associated with dental caries. The cariogenicity of uncooked starch is very low, while that of highly processed and heated starch is higher, but not as high as that of sugar (Moynihan et al., 2004; Sheiham et al., 2001). It is generally accepted that the frequency of sugar intake is more important in the development of caries than the total amount of sugar consumed (Anderson et al., 2009; Burt et al., 2001).

There are currently no scientific studies to prove that recommendations to reduce sugar consumption actually lead to a significant reduction in caries. In dental practice, it is common to advise patients to reduce their sugar intake and to consume sugar less frequently, although the direct effect of these recommendations on caries prevalence has not been adequately investigated (Lingström et al., 2003).

Sugar substitutes (polyols) such as sorbitol and xylitol or artificial sweeteners such as cyclamate and aspartame are available as alternatives to sugar. These substances, such as cyclamate and aspartame, are produced synthetically and are used to reduce calories (Matsukubo et al., 2006; Van Loveren, 2004). Another advantage is that they cannot be metabolized by bacteria in the oral cavity, which means that they do not contribute to acid formation and the development of caries (Matsukubo et al., 2006; Van Loveren, 2004). Sugar substitutes, such as sorbitol and xylitol, have a lower impact on blood sugar levels than sugar and contain fewer calories. However, some sugar substitutes, such as sorbitol, can be broken down by bacteria in the mouth into acids that can attack tooth enamel after a period of adaptation. Some research has even suggested that xylitol may have anti-caries properties (Holgerson et al., 2007; Mäkinen et al., 2008). However, it is still unclear whether the positive effect of xylitol on caries prevention is due to the substance itself or to the most common form of intake, namely chewing gum. It is biologically plausible that the total or partial replacement of sugar with sugar substitutes or artificial sweeteners may reduce the risk of caries, although there are not yet enough high-quality clinical trials on this topic (Lingström et al., 2003).

In dental counselling, it is important to advise patients not only to reduce their absolute sugar intake, but also to reduce the number of sugary snacks. It should also be emphasized that salivary stimulating foods should be consumed to increase salivary flow (Dawes, 2008).

10.3. The Fluoride as Determinant

One of the cornerstones of caries prevention is the use of various fluoride-containing cariostatic agents. Several meta-analyses have shown that the use of fluoride-containing preparations can lead to a reduction in caries (Marinho et al., 2003; Heijnsbroek et al., 2007; Buzalaf et al., 2011; Gluzman et al., 2013). Fluoride has the ability to influence the balance between the demineralization and remineralization processes in the direction of remineralization (Zimmer, 2000). The regular availability of fluoride at the tooth surface is crucial to counterbalance mineral losses at decreasing pH levels. Therefore, the efficacy of fluoride also depends on the frequency of application (Hellwig et al., 2013).

Fluorides can be applied both systemically and topically. Locally applied fluorides, as used in toothpaste, mouthwashes or special fluoride gels, are particularly effective in preventing caries (Marinho et al., 2003). These fluorides come into direct contact with the teeth and can therefore provide their protecting effect. Systemic fluoride, such as fluoride in drinking water or fluoride tablets, can also contribute to caries prevention but has a less direct effect on the tooth surface (Featherstone, 2000, Ten Cate et al., 2019). According to meta-analyses of reviews and recommendations from international professional societies, a daily fluoride intake of 500 to 1500 ppm from fluoride toothpaste is effective in preventing caries in children and adults (Walsh et al., 2010). The fluoride concentration should be adjusted according to the age group. Fluoride gels also have caries-inhibiting properties, but should only be used at home when children are around six years old and can be spit out safely (Hellwig et al., 2013). In addition, fluoride varnish can be applied to patients several times a year in the dental office, which studies have shown to reduce caries by 47% in permanent teeth and 37% in the primary dentition (Leake, 2001).

Systemically administered fluoride, such as fluoride tablets, fluoridated salt or fluoridated water, may also contribute to caries prevention. The caries-preventive effect of fluoride tablets is controversial and is not considered equivalent to topical fluoride toothpaste (Hellwig et al., 2013). Fluoride tablets lead to systemic absorption of fluoride, which is not universally accepted by all experts. The effectiveness of systemic fluoride also depends on regular and controlled intake. It is important to consider the individual needs and risk factors of each patient to choose the appropriate form of fluoride application and avoid the risk of fluorosis (Hellwig et al., 2013).

10.4. The Pits and Fissure Sealant as Determinant

Pit and fissure sealants are also considered a form of secondary prevention, a minimally invasive approach to caries therapy. Pits and fissures on the occlusal surfaces of newly erupted molars are considered particularly susceptible to caries in children and adolescents. Because pits and fissures are predilection sites for caries, the occlusal surfaces represent only about 15% of the total tooth surface area, yet approximately 80-90% of all carious lesions occur there, mostly during the second caries period between the ages of 12 and 18. This is because self-cleaning by the tongue, cheek and sliding of food is reduced in this area. The morphology of the fissure correlates with caries susceptibility and severity. Low-viscosity resins can effectively seal these fissures (Azarpazhooh and Main, 2008), making oral hygiene easier (Ahovuo-Saloranta et al., 2013).

The fundamental aim of sealants is to provide a bacteria-tight seal of these retention areas for plaque with suitable fissure sealants to prevent access of carious substrate and microorganisms.

In principle, three types of sealants can be distinguished:

A) Preventive sealing, in which the enamel of the fissure is sealed with a restorative material without prior preparation.
B) Therapeutic sealing, a therapy in which fissures with incipient enamel caries are sealed.
C) Extended sealing, a preventive sealing of teeth where the carious defect is close to the dentinal border.

If the dentist suspects an increased risk of caries development or progression, sealing should be performed approximately 2-4 years after the eruption of the teeth in question.

Several systematic reviews and expert recommendations have shown that the use of fissure sealants in the molar region has a positive effect on caries prevention (Beauchamp et al., 2008). Fissure sealants can prevent the development of caries in fissures and halt the progression of superficial, non-cavitated carious lesions. Although the efficacy of fissure sealants in patients with active caries is clear, reliable data on the caries-reducing effect in patient groups with different caries risks are missing (Ahovuo-Saloranta et al., 2013). The success of fissure sealants depends on proper application (e.g. isolation) and regular check-ups. In certain cases, highly susceptible fissures and pits on premolars, incisors or in adults can also be sealed (Beauchamp et al., 2008).

11.Conclusion

The most recent theory is based on Miller's chemo parasitic theory of 1898. Keyes developed the concept of the 'Keyes loop' in 1962 to illustrate the complex interactions of different factors such as Host, Substrate and Microorganisms in the formation of caries and König added the time factor to this model to indicate that enamel demineralization only occurs when the acid is exposed to the tooth surface for a sufficient period of time.

The development of dental caries is multifactorial and is influenced by several factors, including the Hosts anatomy and saliva, the bacterial microflora in plaque, Substrate and Time, that need to be present simultaneously to initiate the disease process. There are several co-factors contribute to the prevalence of dental caries such as personal factors as well as oral environmental factors.

The main preventive methods to minimize the caries risk including the reduce of plaque through good oral hygiene, fluoridation, a balanced diet and additionally fissure sealants. Effective implementation of preventive measures requires education of the population and promotion of adherence to these measures in daily life.

12.References

Adler, C. J., Browne, G. V., Sukumar, S. & Hughes, T. (2017) *Evolution of the oral microbiome and dental caries.* Curr. Oral Health Rep. 4, 264–269

Agus, H., Un, P., Cooper, M., und Schamschule, R. (1980) *Ionized and bound fluoride in resting and fermenting dental plaque and individualized caries experience*. Archs oral Biol. 25, p. 517,

Ahovuo-Saloranta, A., Forss, H., Walsh, T. et al (2013) *Sealants for preventing dental de- cay in the permanent teeth.* Syst Rev.

Al Omari, I.K., Duaibis, R.B., Al-Bitar, Z.B. et al (2007) *Application of Pont's Index to a Jordanian population.* Eur. J. Orthod. 29, 627–631

Amaechi, B.T. (2012) *Karieskontrolle durch Beeinflussung der Ernährung.* In: Meyer-Lückel H, Paris S, Ekstrand K. Karies. Thieme, Stuttgart, S. 177-194

Anderson, M. (2002) *Risk Assessment and Epidemiology of Dental Caries: Review of the Literature.* Ped Dent 24, 377

Anderson, C.A., Curzon, M.E., Van Loveren, C., Tatsi, C., Duggal, M.S. (2009) *Sucrose and dental caries: a review of the evidence.* Obes Rev; 10 (Suppl.1), 41–54

Aoba, T. (2004) *Solubility Properties of Human Tooth Mineral and Pathogenesis of Dental Caries.* Oral Dis 10, 249

Aparecido Cury, J., De Oliveira, B.H., Pires dos Santos, A.P., Tenuta, L.M.A (2016) *Are fluoride releasing dental materials clinically effective on caries control?*

Arathi, Rao (2012) *Principles and Practice of Pedodontics*. Chapter-07 Dental Caries and its Management

Ash & Nelson (2003) *Wheeler's Dental Anatomy, Physiology, and Occlusion.* 8th edition. Saunders, p. 13

Ashley, F. (1975) *Calcium and phosphorus concentrations of dental plaque related to caries in 11- to 12- year old male subjects*. Caries Res. 9 , p. 351

Attin, T., Hornecker, E. (2005) *Tooth brushing and oral health: how frequently and when should tooth brushing be performed?* Oral Health Prev Dent;3: 135–140

Avery, J.K., Steele, P.F. *(2002) Oral Development and Histology.* Vol. 3 Thieme, Stuttgart

Axelsson, P., Paulander, J., Svärdström, G., Tollskog, G., Nordensten, S. (1993) *Integrated Caries Prevention: Effect of a Needs-Related Prevention Program on Dental Caries in Children.* Caries Res 27, 83

Bader, J.D., Shugars, D.A., Bonito, A.J. (2001) *A systematic review of selected caries prevention and management methods.* Community Dent Oral Epidemiol, 29:399–411

Baier, H. (1972): *Die Wirklichkeit der Industriegesellschaft als Krankheitsfaktor.* In: Mitscherlich, A./Brocher, T./Mering, v. O./Horn, K. (Hg.): Der Kranke in der modernen Gesellschaft. Köln: Kiepenheuer & Witsch. 37-50.

Balakrishnan, M., Simmonds, R. S., Tagg, J. R. (2000) *Dental Caries is a Preventable Infectious Disease.* ADJ 45, 235

Banas, J. A. (2004) *Virulence Properties of Streptococcus Mutans*. Frontiers in Bioscene 9, 1267

Banting, D.W. (2006) *The Diagnosis of Root Caries Archieved.* 2006-09-30 at the Wayback Maschine- Presentation to the National Institute of Health Consensus Development Conference on Diagnosis and Management of Dental Caries Throughout Life, in pdf format, hosted on the National Institute of Dental and Craniofacial Research, p. 19.

Baranova, J., Büchner, D., Götz, W., Schulze, M., Tobiasch E. (2020) *Tooth Formation: Are the Hardest Tissues of Human Body Hard to Regenerate?*

Beauchamp, J., Caufield, P.W., Crall, J.J. et al (2008) *Evidence-based clinical recommendations for the use of pit-and-fissure sealants:* a report of the American Dental Association Council on Scientific Affairs. J Am Dent Assoc; 139: 257–268

Baumeister, Chr. (2005) *Ein unverzichtbares Instrument in der erfolgreichen Prophylaxepraxis: Speicheldiagnostik*. In: Hinz, R. (Hg.): Prophylaxe aktuell. 9. Jg. Herne: Zahnärztlicher Fachverlag. 100-102.

Behrendt, A., Sziegoleit, F., Wetzel, W.-E. (2002) *Karies bei Kleinkindern durch Primärinfektion mit Streptococcus mutans.* Monatsschrift Kinderheilkunde 150, 603

Belli, W. A., Marquis, R. E. (1991) *Adaption of Streptococcus Mutans and Enterococcus Hirae to Acid Stress in Continuous Culture.* Appl and Environ Microb 57, 1134

Benson, P.E, Parkin, N., Dyer, F.M., Germain, P. (2013) Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment

Berlin, T.V. (1953) *Tandrötan, den svenska folktandv°arden och Vipeholmsundersökningen.* En °aterblick. Ett bidrag. In: Sveriges Läkarförbund (Hg.): Svenska Läkartidningen Vol. 22. Stockholm: Sveriges Läkarförbund

Bernard E. (2021) *Prähistorische Primaten mit süßem Zahn.* Auf: wissenschaft.de: September 2021.

Bjorndal, L., Larsen, T., Thylstrup, A. (1997) *A clinical and microbiological study of deep carious lesions during stepwise excavation using long treatment intervals*. Caries Res.; 31(6):411-7.

Bjorndal, L., Larsen, T. (2000) *Changes in the cultivable flora in deep carious lesions following a stepwise excavation procedure.* Caries Res.; 34(6):502-8.

Bjorndal, L., Reit, C., Bruun, G., Markvart, M., Kjaeldgaard, M., Nasman, P., Thordrup, M., Dige, I., Nyvad, B., Fransson, H., Lager, A., Ericson, D., Petersson, K., Olsson, J., Santimano, E.M., Wennstrom, A., Winkel, P., Gluud, C. (2010) *Treatment of deep caries lesions in adults:*

randomized clinical trials comparing stepwise vs. direct complete excavation, and direct pulp capping vs. partial pulpotomy. Eur J Oral Sci.; 118(3):290-7.

Borutta, A., Kneist, S., Chemnitius, P., Hugnagel, S. (2005) *Veränderungen im Ernährungsverhalten und in der Mundgesundheit bei Vorschulkindern.* Oralprophylaxe & Kinderzahnheilkunde 27, 100

Bowden, G.H.W., Hamilton, I.R. (1998) *Survival of Oral Bacteria.* Crit Rev Oral Biol Med 9, 54

Breighton, D., Brailsford, S. (1998) *Lactobacilli and Actinomyces: Their Role in the Caries Process.* In: Stösser, L. (Hrsg.): Kreisdynamik und Kariesrisiko. Quintessenz, Berlin

Brothwell, D.J., Jutai, D.K., Hawkins, R.J. (1998) *An update of mechanical oral hygiene practices: evidence-based recommendations for disease prevention.* J Can Dent Assoc; 64:295–306

Brown, L.J., Selwitz, R.H. (1995) *The Impact of Recent Changes in the Epidemiology of Dental Caries on Guidelines for the Use of Dental Sealants.* J Pub Health Dent 55, 274

Brudevold, F., Steadman, L.T. (1956) *The distribution of lead in human enamel*. *Journal of Dental Research*. 35 (3): 430–437.

Buddecke, E. (1981) *Biochemische Grundlagen der Zahnmedizin.* Vol. 1 Walter de Gruyter, Berlin, New York

Bullinger, M. (1994) *Krankheitsmodelle.* In: Pöppel, E./Bullinger, M./Härtel, U. (Hg.): Medizinische sychologie und Soziologie. London, Glasgow, Weinheim, New York, Tokyo, Melbourne und Madras Chapmann & Hall. 303-307.

Burt B.A., Pai S. (2001) *Sugar consumption and caries ris*k. a systematic review. J Dent Educ ; 65:1017–1023

Buselmaier, W. (2007*) Biologie für Mediziner.* Vol. 10 Springer Verlag

Buzalaf, M.A., Pessan, J.P., Honório, H.M., Ten Cate, J.M. (2011) *Mechanisms of action of fluoride for caries control.* Monogr Oral Sci 23: 97-114

Bürklein, S. (2011) *Kariesdiagnostik in der Zahnheilkunde.* Bayerisches Zahnärzteblatt 2011 Apr; 48(11):54–9.

Byun, R., Nadkarni, M.A., Chhour, K.L., Martin, F.E., Jacques, N.A., Hunter, N. (2004) *Quantitative Analysis of Diverse Lactobacillus Species Present in Advanced Dental Caries.* J Clin Microbiol 42

Chhour, K.L., Nadkarni, M.A., Byun, R., Martin, F.E., Jacques, N.A., Hunter, N. (2005) *Molecular Analysis of Microbial Diversity in Advanced Caries*. J Clin Microbiol 43, 843

Christianens, T., De Backer, D., Burgers J.S., Baerheim A. (2004) *Guidelines, evidence, and cultural factors.*

Cury, J. A., Rebelo, M. A. B. (2000) *Biochemical Composition and Cariogenicity of Dental Plaque Formed in the Presence of Sucrose or Glucose and Fructose.* Caries Res 34, 491

Davies, RM, Davies, GM, Ellwood, RP (2003) *Prevention. Part 4: Toothbrushing: what advice should be given to patients?* Br Dent J; 195:135–141

Dawes, C. and Jenkins G. (1962) *Some inorganic constituents of dental plaque and their relationship to early calculus formation and caries.* Archs oral Biol. 7, p. 161

Dawes, C. (1983) *A mathematical model of salivary clearance of sugar from the oral cavity.* Caries Res 17, 321

Dawes, C. (1990) *Factors influencing salivary flow rate and composition.* In: Edgar WM, O´Mullane DM (eds.): Saliva and dental health: Report of a consensus workshop held at Ashford Castle, Ireland, July 2–5, 1989, 1st ed., Br Dent J Publications, London

Dawes, C. (2008). *Salivary flow patterns and the health of hard and soft oral tissues.* J Am Dent Assoc 139 (suppl): 18-24

De Grauwe, A., Aps, J.K.M., Martens, L.C. (2004) *Early Childhood Caries (ECC)*: What's in a Name? Eur J Paediatr Dent 5, 62

Derkson, G. und Ponti, P. (1982) *Nursing bottle syndrome; prevalence and etiology in a non-fluoridated city.* J. Can. dent. Ass. 48, p. 389

Delgado, A.J., Olafsson, V.G., Donovan, T.E. (2016) *pH and erosive potential of commonly used oral moisturizers.* J Prosthodont 2016 Jan; 25(1):39–43; DOI: 10.1111/jopr.12324.

Dirks, O. B. (1966) *Posteruptive changes in dental enamel.* J. dent. Res 45, p. 503

Dodds, M.W.J., Hsieh, S.C., Johnson, D.A. (1991) *The effect of increased mastication by daily gum–chewing on salivary gland output and dental plaque acidogenicity.* J Dent Res 70, 1474

Dong, C., Dawes, C. (1995) *The effects of blindfolding and blindness on the unstimulated and chewing–gum–stimulated flow rates of whole saliva*. Archs Oral Biol 40 (8): 771–775

Donner, S. (2006) *Zahnreparatur aus der Tube. Chemiker helfen, sich selbst zu heilen.* In: Kohlhammer, K. (Hg.): Bild der Wissenschaft. Leinfelden-Echterdingen: Konradin Medien GmbH. 23.

Donoghue H.D. (1974) *Composition of dental plaque obtained from eight sites in the mouth of a ten-year-old girl.* J. dent. Res. 53, p. 1289, 1974.

Edgar, W. M. (1992) *Saliva: Its Secretion, Composition and Function.* BDJ 172, 196

Eickholz, P. (1996) *Zahnreinigung bei Kindern*. In: Staehle, H.J./Koch, M.J. (Hg.): Kinder- und Jugendzahnheilkunde. Köln: Deutscher Ärzte-Verlag. 90-96.

Ericsson, Y. (1959) *Clinical investigations of the salivary buffering action.* Acta Odont Scand 17, 131

Featherstone, J.D. (2000) *The science and practice of caries prevention.* J Am Dent Assoc 131: 887–899

Featherstone, J.D.B. (2004) *The Continuum of Dental Caries-Evidence for a Dynamic Disease Process.* J Dent Res 83, C39

Featherstone, J.D.B. (2006) *Caries Prevention and Reversal Based on the Caries Balance.* Ped Dent 28, 128

Fejerskov, O., Baelum, V. (1998) *Changes in prevalence and incidence of the major dental diseases.* In: Oral biology at the turn of the century— misconceptions, truths, challenges and prospects. Guggenheim B, Shapiro S, editors. Basel

Fejerskov, O. (2004) *Changing Paradigms in Concepts on Dental Caries: Consequences for Oral Health Care.* Caries Res 38, 182

Felitti, V. (2002). *Belastungen in der Kindheit und Gesundheit im Erwachsenenalter:* Die Verwandlung von Gold in Blei. Psychosom Med Psychother 48: 359-369

Filoche, S., Wong, L., Sissons, C.H. (2010) *Oral biofilms: emerging concepts in microbial ecology.* J Dent Res; 89:8–18

Fleischmann, L. (1921) *Zur Pathogenese der Zahnkaries.* In: Österreichische Gesellschaft für Zahn-, Mund- und Kieferheilkunde (Hg.): Zeitschrift für Stomatologie. Band 19. Wien: Springer. 153-164.

Flink, H. (2007) *Studies on the prevalence of reduced salivary flow rate in relation to general health and dental caries, and effect of iron supplementation.* -published in Swedish dental jounal (2007)

Folwaczny, M., Hickel, R. (2003) *Biofilm - Problem oder Perspektive?* DZZ 58, 648

Friedrich, H. (1983) *Rationalität, Magie und Interesse: Die Medizin als biotechnisches und soziales Handlungssystem.* In: Deppe, H.-U./Gerhardt, U./Novak, P. (Hg.): Medizinische Soziologie. Jahrbuch 3. Frankfurt und New York: Campus. 215-236.

Galan D. und Lynch E. (1993) *Carious lesions on the roots of the teeth: a review for the general practitioner.* Gerodontology, Vol. 10, pp. 59-71

Garland, P. (2024)*Wrigley-oral healthcare program*

Gängler, P., Hoffmann, T., Willershausen, B., Schwenzer, N., Ehrenfeld, M. (2010) *Konservierende Zahnheilkunde und Parodontologie.* Stuttgart: Thieme

Geurtsen. W., Hellwig, E., Klimek, J. (2016) *Kariesprophylaxe bei bleibenden Zähnen – grundlegende Empfehlungen.*

Gluzman, R., Katz, R.V., Frey, B.J., Mc Gowan, R. (2013) *Prevention of root caries: a literature review of primary and secondary preventive agents.* Spec Care Dentist 33: 133-140

Gustafsson B.E., Quensel, C.E., Lanke, L.S., Lundqvist. C., Grahnen, H., Bonow, B.E., Krasse B. (1954) *The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years.*

Gülzow, H.J., Schiffner, U., Bauch, J. (1987). *Milchzahnkaries bei Kindern aus Stormarner Kindergärten 2 Jahre nach Einführung gruppenprophylaktischer Maßnahmen.* Dtsch Zahnärztl Z 42: 44-45

Hamada, S., Slade, H. D. (1980) *Biology, Immunology, and Cariogenicity of Streptococcus Mutans.* Microbiol Rev 44, 331

Hamilton, I. R., Buckley, N. D. (1991) *Adaption by Streptococcus Mutans to Acid Tolerance.* Oral Microbiol Immunol 6, 65

Hannig, C., Hannig, M., Attin, T. (2005) *Enzymes in the Acquired Enamel Pellicle.* Europ J Oral Sci 113, 2

Hannig, M., Joiner, A. (2006) *The Structure, Function and Properties of the Acquired Pellicle.* In: Duckworth, R. (Hrsg.): The Teeth and Their Environment. Karger, Basel, 29.

Hannig, M., Hannig, C. (2007) *Der initiale Biofilm - pathogen oder protektiv?* Oralprophylaxe & Kinderzahnheilkunde 29

Hanson, H. (1961) *Zusammensetzung und Funktion des Speichels.* Dtsch Zahnärztl Z 16, 143

Harper, D. S., Loesche, W. J. (1984) *Growth and Acid Tolerance of Human Dental Plaque Bacteria.* Arch Oral Biol 29, 8

Head, J. (1912) *A study on saliva and its action on tooth enamel in reference to its hardening and softening.* The Journal of the American Medical Association, pp. 2118-2122

Heintze, U., Birkhed, D., Björn, H. (1983) *Secretion rate and buffer effect of resting and stimulated whole saliva as a function of age and sex.* Swed Dent J 7, 227

Heijnsbroek, M., Paraskevas, S., Van der Weijden, G.A. (2007) *Fluoride interventions for root caries.* A review. Oral Health Prev Dent 5: 145-152

Helfenstein, U., Steiner, M., Marthaler, T.M. (1991) *Caries prediction on the basis of past caries including precavity lesions.* Caries Res 25: 372–376

Hellwig, E., Klimek, J., Attin, T. (1999) *Einführung in die Zahnerhaltung.* 3. Auflg. Urban & Fischer, München jena

Hellwig, E., Klimek, J., Attin, T. (2010) *Einführung in die Zahnerhaltung*. 5. Auflage, Köln: Deutscher Zahnärzte Verlag

Hellwig, E., Schiffner, U., Schulte, A. (2013) *Fluoridierungsmaßnahmen zur Kariesprophylaxe.*

Hellwig, E., Schiffner, U., Schulte, A., Koletzko, B., Bergmann, K., Przyrembel, H. (1983) *S2K-Leitlinie Fluoridierungsmaßnahmen zur Kariesprophylaxe*. AWMF Re- gister Nr. 083–001

Holgerson, P.F., Sjöström, I., Stecksen-Blicks, C., Twetman, S. (2007) *Dental plaque formation and salivary mutans streptococci in schoolchildren after use of xylitol-containing chewing gum.* Int J Paed Dent 17: 79–85

Holloway, P.J. (1983) *The role of sugar in the etiology of dental caries.* Journal of Dentistry, 11, 189-213.

Horowitz, A.M. (2004) *A report on the NIH consensus development conference on diagnosis and management of dental caries throughout life. J Dent Res* 83(Spec Iss C): C15–C17.

Höf, H., Dörries, R. (2005*) Medizinische Mikrobiologie*. Vol. 3. Georg Thieme Verlag, Stuttgart

Humphrey, S.P., Williamson, R.T. (2001) *A Review of Saliva: Normal Composition, Flow, and Function.* J Prosthet Dent 85, 162

Hunter, D.J. (1995) *Consensus Methods For Medical and Health Services Resarch*

Jenkins, G.N., Edgar, W.M. (1989) *The effect of daily gum–chewing on salivary flow rates in man.* J Dent Res 68, 786

Johansson, I., Saellström, A-K., Rajan B.P., Parameswaran, A. (1992) *Salivary flow and dental caries in indian children suffering from chronic malnutrition.* Caries Res 26, 38

Karpiński, T. M., Szkaradkiewicz, A. K. (2013) *Microbiology of dental caries.* J Biol Earth Sci : 3(1):M21–4.

Keegan R. Selig & Mary T. Silcox (2021) *The largest and earliest known sample of dental caries in an extinct mammal (Mammalia, Euarchonta, Microsyops latidens) and its ecological implications*

Kemp, A. (2003) *Dental and skeletal pathology in lungfish jaws and tooth plates. Alcheringa: An Australas. J. Palaeontol.* 27, 155–170

Kenney, E.B., und Ash, M.M. (1969) *Oxidation-reduced potential of developing plaque, periodontal pockets and gingival sulci.* J. Periodont. 40, p. 630

Klimek, J., Hellwig, E. (1999) *Kariesätiologie und -diagnose.* In: Heidemann, D. (Hrsg.): Kariologie und Füllungstherapie. Urban & Fischer Verlag, München

Klussmann, W. (1936) *Gebissverfall und Ernährung*. Stuttgart und Leipzig: Hippokrates.

Kneist, S. (1998) *Begleitphänomene in der mikrobiologischen Speicheldiagnostik.* Oralprophylaxe 20, 208

Koch, M.J. (19992): *Zähne und Ernährung.* In: Biesalski, H.-K. (Hg.): Ernährungsmedizin. Stuttgart: Thieme. 437-447.

Kolenbrander, P.E., Palmer, R.J., Rickhard, A.H. (2006) *Bacterial Interaction and Successions During Plaque Development.* Periodontology 2000 42, 47

Koulourides, T. (1966). *Dynamics of Tooth Surface Oral Fluid Equilibrium*. In: Staple P (Hg.) Advances in Oral Biology. Aufl. Academic Press, Inc, New York, S. 149- 171

König, K.G. (1971): *Karies und Kariesprophylaxe.* München: Goldmann.

König, K. G. (1987) *Karies und Parodontopathien - Ätiologie und Prophylaxe*. Vol. 1 Georg Thieme Verlag, Stuttgart, New York

König KG (1991) *Die Bedeutung des Speichels für die Mund- und Zahngesundheit.* In: Dentalforschung: der flüssige Zahn – stimulierter Speichelfluß, die neue Chance in der Kariesprophylaxe. Wrigley GmbH (Herausgeber), Frankfurt a. M.

König, K. G. (1992) *Ursachen der Karies.* In: Ketterl, W. (Hrsg.): Praxis der Zahnheilkunde 2 Zahnerhaltung I. Urban & Fischer Verlag, München, 1.

König, K.G. (1999) *Die Bedeutung des Speichels für die Mund und Zahngesundheit.* In: DAJ: Ernährung und Mundgesundheit. Hintergründe und Umsetzungsmöglichkeiten im Rahmen der Gruppenprophylaxe. Hürth: Greven & Bechtold. 139-144.

König, K. G. (2000) *Diet And Oral Health.* Int Dent J 50, 162

Krasse, B. (1986) *Die Quintessenz des Kariesrisikos.* Quintessenz, Berlin

Krüger, W., Mausberg, R., Kozielski, PM. (1978) *Kariesfrequenz, Kariesbefall und soziale Milieubedingungen bei Kindern im Vorschulalter.* Dtsch Zahnärztl Z 33: 164–166

Kumar, P.S., Mason, M.R. (2015): *Mouthguards: does the indigenous microbiome play a role in maintaining oral health?* Front Cell Infect Microbiol 2015 May; 5:35; DOI: 10.3389/fcimb.2015.00035.

Kuramitsu, H.K. (1993) *Virulence Factors of Mutans Streptococci: Role of Molecular Genetics.* Crit Rev Oral Biol Med 4, 159

Künzel, W. (1997) *Caries decline in Deutschland.* Eine Studie zur Entwicklung der Mundgesundheit. Vol. 1 Hüthig Verlag, Heidelberg

Larsen, M.J., Jensen, A.F., Madsen, D.M., Pearce, E.I.F. (1999) *Individual Variations of pH, Buffer Capacity, and Concentrations of Calcium and Phosphate in Unstimulated Whole Saliva.* Arch Oral Biol 44, 111

Leake, J.L. (2001) *Clinical decision-making for caries management in root surfaces.* J Dent Educ; 65:1147–1153

Leander-Lumikari, M., Loimaranta, V. (2000) *Saliva and Dental Caries.* Adv Dent Res 14, 40

Lehmann, K. M., Hellwig, E. (2005) *Zahnärztliche Propädeutik.* Vol. 10 Urban & Fischer Verlag, München

Lendenmann, U., Grogan, J., Oppenheim, F. G. (2000) *Saliva and Dental Pellicle,* A Review. Adv Dent Res 14, 22

Lingström, P., van Houte, J., Kashket, S. (2000) *Food Starches and Dental Caries.* Crit Rev Oral Biol Med 11, 366

Lingström, P., Holm, A.K., Mejáre, I., Twetman, S. et al. (2003) *Dietary factors in the prevention of dental caries:* a systemic review. Acta Odontol Scand; 61: 331–340

Listgarten, M.A. (1994) *The Structure of Dental Plaque.* Periodontology 2000 5, 52

Loesche, W. J. (1986) *Role of Streptococcus Mutans in Human Dental Decay.* Microbiol Rev 50, 353

Lovell, N.C. (1991) *An evolutionary framework for assessing illness and injury in nonhuman primates.* Am. J. Phys. Anthropol.34, 117–155

Löffler, G., Petrides, P.E. (1990) *Physiologische Chemie.* 4. Aufl., Springer-Verlag, Berlin, Heidelberg, New York

Lundeen, T., Sturdevant, J., Sluder. T.B. (1995) *Clinical significance of dental anatomy, histology, physiology, and occlusion.* In: C.M. S (Hg.) The Art and Science of Operative Dentistry. 3 ed. Aufl. Mosby, St Louis, S. 10- 59

Matsukubo, T., Takazoe, I. (2006) *Sucrose substitutes and their role in caries prevention*. Int Dent J; 56:119–130

Margolis, H.C., Moreno, E.C., Murphy, B.J. (1985) *Importance of high pKA acids in cariogenic potential of plaque.* J Dent Res 64, 786

Marinho, V.C., Higgins, J.P., Sheiham, A., Logan, S. (2003) *Fluoride toothpastes for preventing dental caries in children and adolescents.* Cochrane Database Syst Rev

Marsh, P. D. (1999): *Microbiologic aspects of dental plaque and dental caries.* Dent Clin North

Marsh, P., Martin, M.V. (2002) *Orale Mikrobiologie.* Vol. 1 Georg Thieme Verlag, Stuttgart

Marsh, P.D. (2003) *Are Dental Diseases Examples of Ecological Catastrophes?* Microbiology 149, 279

Marsh, P. D. (2004) *Dental Plaque as a Microbial Biofilm.* Caries Res 38, 204

Marsh, P. D. (2005) *Dental Plaque: Biological Significance of a Biofilm and Community Life-Style.* Journal Clin Periodontol 32, 7

Martin, E.S und Wittenberger, C. (1979) *Characterization of a phosphoenolpyruvate-dependent sucrose phosphotransferase system in Streptococcus mutans*. Infect. Immunity 24, p. 865

Mäkinen, K.K., Alanen, P., Isokangas, P., Isotuüpa, K., Söderling, E., Mäkinen, P.L., Wenhui, W., Weijian, W., Xiaochi, C., Yi., Boxue, Z. (2008). *Thirty-nine-month xylitol chewing-gum programme in initially 8-year-old schoolchildren: A feasibility study focusing on mutans streptococci and lactobacilli.* Int Dent J 58: 41 – 50

Mead, M. (1972) *Kulturbegriff und psychosomatische Medizin.* In: Mitscherlich, A./Brocher, T./ Mering, v. O./Horn, K. (Hg.): Der Kranke in der modernen Gesellschaft. Köln: Kiepenheuer & Witsch. 111-139.

Meurman, J.H., Rantonen, P. (1994) *Salivary flow rate, buffering capacity, and yeast counts in 187 consecutive adult patients from Kuopio*. Finland. Scand J Dent Res 102, 229

Meyer, W. (1951) *Anatomie.* In: Port, G./Euler, H. (Hg.): Lehrbuch der Zahnheilkunde. München: Bergmann. 1-120.

Meyer-Lückel H., Paris S. und Ekstrand K. (2012) *Karies.* Wissenschaft und Klinische Praxis, New York: Thieme,

Miller, W.D. (1889) *Die Mikroorganismen der Mundhöhle. Die örtlichen und allgemeinen Erkrankungen, welche durch dieselben hervorgerufen werden.* Leipzig: Thieme.

Miller, W. D. (1893) *Agency of Microorganisms in Decay of Human Teeth.* Dental Cosmos 25, 1

Moynihan, P., Petersen, P.E. (2004) *Diet, nutrition and the prevention of dental diseases.* Public Health Nutr; 7:201–226

Mundorff, S. A., Eisenberg, A. D., Leverett, D. H., Espeland, M. A., Proskin, H. M. (1990) *Correlation between Numbers of Microflora in Plaque and Saliva*. Caries Res 24, 312

Nanninga, C., Steinhauser, U., Schoop, B., Wernisch, J., Sperr, W. (1996*) Dentinrauhtiefe in Abhängigkeit von Borstenhärte und Bürstenprofil. Abrasivität von Zahnbürsten.* In: Drücke, W. (Hg.): Phillip Journal. 13. Jg. Bd. 9-10. München: Neuer Merkur. 289-294.

Naujoks, R., Bramstedt, F., Ranke, E., Auerbach, M. (1961) *Zur Problematik der Speichelgewinnung für biochemische Untersuchungen.* Deutsche Zahnärzte Z 16, 171 (1961)

Naumova, E. A. et al. (2012*) Fluoride bioavailability in saliva and plaque.* BMC Oral Health 2012 Jan; 12:3; DOI: 10.1186/1472-6831-12-3.

Neville, B.W., Damm D., Allen C., Bouquot J. (2002) *Oral & Maxillofacial Pathology.* 2nd edition

Newburn, E. (1992) *Preventing Dental Caries: Breaking the Chain of Transmission.* JADA 123, 55

Nikiforuk, G. und Fraser, D. (1979) *Etiology of enamel hypoplasia and interglobular dentin: the roles of hypocalcemia and hypophosphatemia.* Metab. Bone Dis. Rel. Res. 2, p. 17

Nikiforuk G. (1985) *Understanding Dental Caries. Vol. 1: Etiology and Mechanisms.* Bd. 1, New York: Karger,

Nikiforuk, G. (1985) *Understanding Dental Caries: Etiology and Mechanisms, Basic and Clinical Aspects: Prevention, Basic and Clinical Aspects.* Vol. 2 Karger, Basel

Novak, P. (1994) *Erklärungsmodelle von Krankheit und Kranksein.* In: Wilker, F.-W./Bischoff, C./Novak, P. (Hg.): Medizinische Psychologie Medizinische Soziologie. München, Wien und Baltimore: Urban & Schwarzenberg. 195-200.

Oeschger, U. (2006) *Der Einfluss ausgesuchter Speichelproteine auf die Demineralisation von bovinem Zahnschmelz-eine In-vitro-Studie.* Diss. Freiburg i. Br.: Albert-Ludwigs Universtät.

Ommerborn, M., Raab, W. (2005) *Allgemeinerkrankungen und Schäden der Zahnhartsubstanzen.* -eine Übersicht- In: Hinz, R. (Hg.): Prophylaxe aktuell. 9.Jg. Herne: Zahnärztlicher Fach-V erlag. 66-73.

O´Reilly M.T., De Jesus V.J., Hatch, J.P. (2013) *Effectiveness of a sealant compared with no sealant in preventing enamel demineralization in patients with fixed orthodontic appliances.* A prospective clinical trial

Orland, F.J., Blayney, J.R., Harrison, R.W. (1954) *Use of the germfree animal technic in the study of experimental dental caries. I. Basic observations on rats reared free of all microorganisms.* In: International Association for Dental Research (Ed.): J. Dent. Res. Alexandria: International and American Association Research. 147-174.

Paes Leme, A. F. et al. (2008) *Effects of sucrose on the extracellular matrix of plaque-like biofilm formed in vivo, studied by proteomic analysis.* Caries Res 2008; 42(6):435–43;

Page, L. und Friend B. (1974*) Level of use of sugars in the United States*. Sugars in nutrition, p. 93,

Pickerill, H.P. (1924) *The Prevention of Dental Caries and Oral Sepsis.* Toronto, Canada: The MacMillan;

Pilz, W. (1980) *Mundhöhlenmilieu.* In: Pilz, W./Plathner, C.H./Taatz, H. (Hg.): Grundlagen der Kariologie und Endodontie. München und Wien: Hanser. 121-172.

Pitts, N.B. (2001) *Clinical diagnosis of dental caries.* A European perspective. J Dent Educ 65: 973–980.

Pitts, N.B., Ekstrand, K.R., ICDAS Foundation (2013) *International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) – methods for staging of the caries process and enabling dentists to manage caries.* Community Dent Oral Epidemiol 2013 Feb; 41(1):e41–52. DOI: 10.1111/cdoe.12025.

Preston, G., Berkowitz, R. und Forrester, D. (1977) *Nursing bottle caries.* Pediatrics, Springfield 59, p. 777, 1977.

Prochaska J.O., Velicer W.F. (1997) *The transtheoretical model of behavior change.* Am J Health Promotion 12: 38–48

Prophylaxe Impuls (2005) *Mineralien in Limonade könnten Zähne schonen.* In: Hinz, R. (Hg.): Prophylaxe aktuell. 9. Jg. Herne: Zahnärztlicher Fachverlag. 30.

Psoter, W.J., Reid, B.C., Katz, R.V. (2005) *Malnutrition and Dental Caries*. A Review of the Literature. Caries Res 39, 441

Puy, C. L. (2006) *The Role of Saliva in Maintaining Oral Health and as an Aid to Diagnosis.* Medicina Oral, Patologia Oral y Cirugia Bucal 11, 55

Rethman, M.P., Beltrán-Aguilar, E.D., Billings, R.J. et al. (2011) *Non-fluoride caries preventive agents – Full report of a systematic review and evidence-based recommendations.* A Report of the Council on Scientific Affairs (2011)

Rheinwald, U. (1956): *Die Karies der Zähne als Korrosionserscheinung.* Eine Ätiologische Studie. In: Wannenmacher, E. (Hg.): Sammlung Meusser. Abhandlungen aus dem Gebiete der klinischen Zahnheilkunde. Heft 39. Leipzig: Barth.

Ribeiro, C.C.C., De Oliveira Lula, E.C., DA Costa R.C.N., Nunes A.M.M. (2012) *Rationale for the partial removal of carious tissue in primary teeth.* Pediatr Dent.; 34(1):39-41.

Ricketts, D., Lamont, T., Innes, N.P., Kidd, E., Clarkson, J.E. (2013) *Operative caries management in adults and children*. Cochrane Database Syst Rev. (3):Cd003808.

Riethe, P. (1985): *Konservierende Zahnheilkunde.* In: Schwenzer, N. (Hg.): Zahn-Mund-Kiefer-Heilkunde. Bd. 4. Konservierende Zahnheilkunde und Mundschleimhauerkrankungen. Stuttgart: Thieme. 1-360.

Ripa, L. (1978) *Nursing habits and dental decay in infants: 'nursing bottle caries.* J. Dent. Child. 45, p. 274,

Ritz, H.L. (1967) *Microbial population shifts in developing human dental plaque.* Archs oral Biol. 12, p. 1561,

Rosan, B., Lamont, R. J. (2000) *Dental Plaque Formation.* Microbes and Infection 2, 1599

Rosenhek, M., Macpherson, L.M.D., Dawes, C. (1993) *The effects of chewing gum stick size and duration of chewing on salivary flow rate and sucrose and bicarbonate concentrations.* Archs Oral Biol 38, 885 (1993)

Rozeik, R., Herrmann, M. (1961): *Über den Einfluß der Azidose und Alkalose auf die Kariesentstehung.* In: Organ der Deutschen Gesellschaft für Zahn-, Mund- und Kieferheilende (Zentralverein) (Hg.): DZZ. 16. Jg. Heft 4. München: Hanser. 344-349.

Rupf, S., Jentsch, H., Eschrich, K. (2007) *Mikroorganismen und orale Erkrankungen: Lebensraum Mundhöhle.* Biologie in unserer Zeit 37, 51

Sambunjak, D., Nickerson, J.W., Poklepovic T. et al. (2011) *Flossing for the management of periodontal diseases and dental caries in adults.* Cochrane Database Syst Rev

Sbordone, L., Bortolaia, C. (2003) *Oral microbial biofilms and plaque-related diseases: microbial communities and their role in the shift from oral health to disease.* Clin Oral Invest; 7:181–188

Screebny, L.M. (1982) *Sugar availability, sugar consumption and dental caries.* Community Dent Oral Epidemiol; 10:

Selwitz, R.H., Ismail, A.I., Pitts, N.B. (2007) *Dental Caries.* The Lancet 369, 51

Sheiham, A. (2001) *Dietary effects on dental diseases.* Public Health Nutr; 4: 569–591

Sicilia, A., Arregui, I., Gallego, M., Cabezas, B., Cuesta, S. (2002) *A systematic review of powered vs.manual toothbrushes in periodontal cause-related therapy.* J Clin Periodontol; 29(Suppl.3): 39–54

Silverman, G. und Kleinberg, I. (1967) *Fractionation of dental plaque and the characterization of cellular and acellular components.* Archs oral Biol. 12, p. 1387

Scheinin, A., Mäkinen, K.K., Ylitalo, K. (1976). *Turku sugar studies. V. Final report on the effect of sucrose, fructose and xylitol diets on the caries incidence in man.* Acta Odontol Scand 34: 179-216

Schiffner, U. (1997) *Der Einfluss von Speichelproteinen auf die Demineralisation von Zahnschmelz Untersuchung in einer künstlichen Mundhöhle.* Vol. 1 Karl Hanser Verlag, München, Wien

Schiffner, U. (2016) *Krankheits- und Versorgungsprävalenzen bei Kindern (12-Jährige): Karies, Erosionen, Molaren-Inzisiven-Hypomineralisationen.* In: Jordan AR, Micheelis W (Gesamtbearbeitung): Fünfte Deutsche Mundgesundheits-Studie (DMS V). Dtsch Ärzte- Verlag, Köln, S. 231-268

Schmidt, H. (1974) *Remineralisation und morphologische Strukturen des entkalkten menschlichen Zahngewebes. In: Miles, A.E.W. (Ed.): Arch. Oral Biol. London: Pergamon Press. 131-137.*

Schmoeckel, J. et al. (2020) *Vor jeder Therapie steht die (frühe) Diagnose.* Bayerisches Zahnärzteblatt 2020 Dec; 57(12):42–9.

Schroeder, H. und Boever, J.D. (1970) *The structure of microbial dental plaque*. Edinburgh: Livingstone , p. 49.

Schroeder, H.E. (1991): *Pathobiologie oraler Strukturen. Zähne, Pulpa, Parodont.* Zum Beispiel Basel, München und Paris: Karger.

Schroeder, H. E. (1997) *Pathobiologie oraler Strukturen*. Vol. 3Basel

Schroeder, H. E. (2000) *Orale Strukturbiologie.* Vol. 5 Georg Thieme Verlag, Stuttgart

Schumacher, G.-H., Schmidt, H., Börning, H., Richter, W. (1990) *Anatomie und Biochemie der Zähne.* Stuttgart und New York: Fischer.

Schwenzer, N., Ehrenfeld, M. (2000) *Allgemeine Chirurgie* Band 2. Vol. 3 Georg Thieme Verlag, Stuttgart, New York

Shannon, I.L. (1966) *Climatological effects on human parotid gland function.* Archs Oral Biol 11, 451

Shannon, I.L. (1968) *Specific gravity of oral fluids.* Tex Rep Biol Med 26, 349

Shannon, I.L. Frome, W.J. (1973) *Enhancement of salivary flow rate and buffering capacity.* J Canad Dent Assoc 3, 177

Sheiham, A. (2001) *Dietary Effects on Dental Diseases.* Publ Health Nutr 4, 569

Silverstone, L.M. (1983). *Remineralization and dental caries: new concepts*. Dental Update, 10, 261-273.

Slot, D.E., Vaandrager, N.C., Van Loveren, C., Van Palenstein, Helderman W.H., Van der Weijden G.A. (2011) *The effect of chlorhe- xidine varnish on root caries*. a systematic review. Caries Res; 45: 162–173

Slot, D.E., Wiggelinkhuizen, L., Rosema, N.A.M., Van der Weijden G.A. (2012) *The efficacy of manual toothbrushes following a brushing exercise: a systematic review.* Int J Dent Hygiene; 10:187–197

Smith, P.M. (1996) *Mechanisms of secretion by salivary glands.* In: Edgar WM, O´Mullane DM (eds.): Saliva and oral health, 2nd ed., Br Dent J Publications, London

Socransky, S.S., Manganiello, S.S., Propas, D., Oram V. und Houte, J.V. (1977) *Bacteriological studies of developing supragingival plaque.* J. periodont. Res. 12, p. 90,

Sonis, Stephen T. (2003) *Dental Secrets: Questions and Answers Reveal the Secrets to the Principles and Practice of Dentistry.* 3rd edition. Hanley & Belfus, Inc

Spatafora, G. A., Sheets, M., June, R. (1999) *Regulated Expression of the Streptococcus mutans dlt Genes Correlates with Intracellular Polysaccharide Accumulation.* J Bacteriol 181, 2363

Sreebny, L.M. (1996) *Xerostomia: diagnosis, management and clinical complications.* In: Edgar WM, O´Mullane DM (eds.): Saliva and oral health, 2nd ed., Br Dent J Publica- tions, London

Starck, D. (1979) *Vergleichende Anatomie der Wirbeltiere auf evolutionsbiologischer Grundlage.* Berlin, Heidelberg und New York: Springer.

Steinberg, D., Poran, S., Shapira, L. (1999) *The Effect of Extracellular Polysaccharides from Streptococcus mutans on the Bactericidal activity of Human Neutrophiles.* Arch Oral Biol 44, 437

Steinle, K. (2003) *Klinisch-experimentelle Studie über die Auswirkungen zweier Handzahnbürsten auf die Gingiva sowie in Bezug auf die Plaquereduktion an den Zahnoberflächen.* -Diskussion verschiedener Bewertungsmethoden. Diss. München: Ludwig-Maximilians-Universität.

Stößer, L. (1993) *Kariesprophylaxe beginnt im Milchgebiß.* In: Banaschewski, P. (Hg.): Zahnärztliche Praxis. 11. Gräfelfing bei München: Werk. 430-432.

Summit, James B.,J. Robbins W., and Schwartz R.S. (2001) *Fundamentals of Operative Dentistry.* A Contemporary Approach. 2nd edition. Carol Stream, Illinois, Quintessence Publishing Co, Inc,p. 30.

Sutherland, I.W. (1999*) Biofilm Matrix Polymers -Role in Adhesion.* In: Newman, H. N., Wilson, M. (Hrsg.): Dental Plaque Revisited - Oral Bio- films in Health and Disease. Bioline, University London

Sutherland, I.W. (2001) *The Biofilm Matrix Polymers - an Immobilized but Dynamic Microbial Environment.* Trends Microbiol 9, 222

Svensaeter, G., Larsson, U.B., Greif, E.C.G. (1997) *Acid Tolerance Response and Survival by Oral Bacteria.* Oral Microbiol Immunol 12, 266

Taatz, H. (1980) *Zahnkaries.* In: Pilz, W./Plathner, C.H./Taatz, H. (Hg.): Grundlagen der Kariologie und Endodontie. München und Wien: Hanser. 15-119

Tacha, M. (1999) Zähne. Vorsorge, Behandlung, Kosten. Wien

Ten Cate, J.M., Larsen, M., Pearce, E. (2003) *Chemical interactions between the tooth and oral fluids.* In: Fejerskov O (Hg.) Dental caries. Aufl. Blackwell Munsksgaard, Oxford, S. 51- 61

Ten Cate, J.M., Buzalaf, M.A.R. (2019) *Fluoride mode of action: once there was an observant dentist.* J Dent Res 98: 725–730

Tennert, C., Meyer-Lückel, H. (2019): *Karies, dentaler Biofilm und Ernährung.* DFZ 2019 Apr; 63(4):74–83; DOI: 10.1007/s12614-019-7825-0.

Towle, I., Irish, J. D., Groote, I. D. & Fernée, C. (2019) *Dental caries in human evolution: frequency of carious lesions in South African fossil hominins.* bioRxiv.

Twetman S. (2004) *Antimicrobials in future caries control?* A review with special re- ference to chlorhexidine treatment. Caries Res; 38:223–229

Vale, G. C. et al. (2007*) Temporal relationship between sucrose-associated changes in dental biofilm composition and enamel demineralization.* Caries Res 2007; 41(5):406–12; DOI: 10.1159/000105764.

Van der Sanden, Wil J.M., Mettes Drik G., Plasschaert A.J.M., Verdonschot E.H. (2003) *Clinical practice guidelines in dentistry: Opinions of dental practitioners on their contribution to the quality of dental care*

Van Loveren, C. (2004) *Sugar alcohols: What is the evidence for caries-preventive and caries-therapeutic effects?* Caries Res; 38:286–293

Van Nieuw Amerongen, A., Bolscher, J. G. M., Veerman, E. C. I. (2004) *Salivary Proteins: Protective and Diagnostic Value in Cariology?* Caries Res 38, 247

Van Rijkom, H.M., Truin, G.J., Van't Hof M.A. (1996) *A meta-analysis of clinical studies on the caries-inhibiting effect of chlorhexidine treatment.* J Dent Res; 75:790–795

Vogel, G.L. (2011) *Oral fluoride reservoirs and the prevention of dental caries.* Monogr Oral Sci

Walsh, T., Worthington, H.V., Glenny, A.M., Appelbe, P., Marinho, V.C., Shi, X. (2010) *Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents.* Cochrane Database Syst´

Weidenauer, H. (2001) *Speichel als Keimüberträger.* Laryngo-Rhino-Otol 80, 26

Wennhall, I., Matsson, L., Schröder, U., Twetman, S. (2008) *Outcome of an oral health outreach programme for preschool children in low socioeconomic multicultural area.* Int J Paed Dent 18:84-90

Wetzel, W.-E., Böhmer, C., Sziegoleit, A. (1997) *In-vitro-Karies durch Candida albicans.* Acta Medica of Dental Helvetica 2, 308

Whelton, H. (1996) *The anatomy and physiology of salivary glands.* In: Edgar WM, O´Mullane DM (eds.): Saliva and oral health, 2nd ed., Br Dent J Publications, London

Wiedemann, W. (1993) *Zähne-ihre Funktion und Gesunderhaltung.* In: DAJ (Hg.): Zahngesundheitserziehung in der Grundschule. Hürth: Greven & Bechtold. 10-21.

Wikner, S., Söder, P–Ö. (1994) *Factors associated with salivary buffering capacity in young adults in Stockholm, Sweden.* Scand J Dent Res 102, 50

Williams, K., Schemehorn, B., McDonald, J., Stookey, G.und Katz, S. (1982) *Influence of selected fatty acids upon plaque formation and caries in the rat.* Archs oral Biol. 27, p. 1027,

World Health Organization (1946) *Constitution of the World Health Organization*

Wright, G.Z., Banting, D.W., Feasby, W.H. (1979) *The Dorchester dental flossing study: final report.* Clin Prev Dent; 1: 23–26

Yüksel, S. (2010) *Karieserfahrung bei Kleinkindern – Korrelation zu verschiedenen Ernährungs- und Prophylaxeparametern.* Med Diss, Marburg

Zimmer, S. (2000) *Kariesprophylaxe als multifaktorielle Präventionsstrategie.* Habilitationsschrift. Berlin: Humboldt Universität.