Chapter 5

Folate in Dentistry

Aysan Lektemur Alpan and Nebi Cansin Karakan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74055

Abstract

Balanced nutrition is the key point of a healthy life includes intake of vitamins and minerals. Vitamins such as folate (B9) have an important role in system homeostasis. Vitamin B derivatives, also folate are water-soluble vitamin class which plays a key role in cell metabolism. Folate is necessary to produce new cells via stimulating DNA and RNA methylation. Folate has positive effect on recurrent aphthous stomatitis, gingival hyperplasia, preventing early childhood caries and periodontal diseases. Alveolar bone and periodontal ligament development are related to sufficient concentrations of folate. Folate reduces gum bleeding, and increases osteoblastic activity and bone mineral density, also decreases osteoclastic activity. Effect on DNA and RNA metabolism causes the reduction of reactive oxygen species. In early stages of pregnancy, folate deficiency may cause birth anomalies due to neural tube defects such as lip, alveolar and palatal clefts. Folate deficiency effects on DNA and RNA metabolism negatively. DNA and RNA repair, production and methylation system is being interrupted. Therefore chromosal abnormalities occur and that situation may cause cancer and leukemia. Folate is mainly provides systemic homeostasis and important for maintaining chromosomal activities. Consequently adequate concentrations of folate must be taken regularly.

Keywords: gum disease, dentistry, folate

1. Introduction

Factors such as nutrition, heredity and environmental conditions are affecting human health. Poor diet and sedentary lifestyle are among the main causes of morbidity and mortality worldwide. Recent developments in nutritional science show that diet may have an important role not only in maintaining optimum health, but also in reducing the risk of some diseases. It is necessary for people to have a healthy and balanced diet for healthy life, body growth, renewal, development and work. Otherwise, the nutrients needed for the body are not taken

in time and in sufficient quantities, so the resistance to the diseases decreases and the treatment of the diseases becomes long, difficult and expensive. The importance of vitamins and minerals in balanced nutrition is better understood in the 20th century. The evaluation of food is made according to the chemical composition they contain. In this way, the needs of a human body can be determined by biochemical concepts. The ingredients of the foods include carbohydrates, proteins, fats, minerals, vitamins and water from the basic compound ingredients. Studies showed that; those who consume fruits and vegetables regularly are found to be at a lower risk than those who consume less in terms of the risk of developing cancer [1]. Adequate nutrition is an integral part for maintaining good oral health. There is a constant synergy between nutrition and the integrity of the health and ill mouth cavity. There is also an interdependent relationship between them: nutrition affects oral health, and oral health affects nutrition [2]. It has been reported that the consumption of fruits and vegetables reduces mouth, esophagus, lung, stomach, colorectum, larynx, pancreas, breast and prostate cancer [3]. In addition to their liquid and pulp content, fruits and vegetables are important for the high levels of vitamins and minerals they contain. In particular, the antioxidant properties of vitamin A, E, vitamin C and β-carotene for fruits and vegetables are the best sources and most studied vitamins for oral health. Besides these vitamins, vitamins B6, folate, vitamin K, vitamin E and niacin content are also important.

Vitamin B complex is a water-soluble vitamin class that plays an important role in cell metabolism. Eight vitamins which are different from each other in terms of their chemical composition and pharmacological properties create this family [4]. Folate which is called "folium" means leaf, is one of the vitamins of group B, dissolved in water and was first separated from natural foods in 1943. Folate is involved in single carbon metabolism in the body, providing single carbon unit for purine and thymidylate synthesis and essential biologic product for deoxyribonucleic acid (DNA) and neurotransmitters methylation such as phospholipids, proteins. Thus, the construction of nucleic acids and the conversion of some amino acids to each other (conversion of serine, glycine and homocysteine to methionine, glutamic acid catabolism of histidine) are achieved [5]. Folate stands out as a molecule having biological importance in recent years. Folate is a water-soluble vitamin in the structure of pteroylglutamic acid composed of pteridine, p-aminobenzoic acid and glutamic acid. Folate is mainly involved in important biochemical events such as the metabolism of purines and pyrimidine homocysteine and methionine amino acids. Folate is essential to produce and maintenance of new cells and DNA, **ribonucleic acid** (RNA) synthesis through methylation [6]. It is a carrier of 1-carbon parts (methyl and formyl groups) in the cells, and acts role for the synthesis of human macromolecules for example methionine, deoxythymidylate monophosphate, and purines [7].

Lentil, green vegetables, citrus fruits, sparrowgrass, dried beans, broccoli, sunflower seeds, cereal, avocado and tomato juice contain high amounts of folate. In case of gastrointestinal, kidney or liver function deficiency, as well as an urinary problem, folate excretion may increase and folate deficiency occurs. Also an inflammation due to any disease can reduce folate concentration. Cancer and anemia negatively effect on folate metabolism. Forgetfulness, dizziness, overstrain and shortness of breath can be the symptoms of folate deficiency. Regular clinical visits and blood test assessments are important to diagnose the deficiency. The estimated

average requirement for folate is 320 μg/day and the recommended dietary allowance value is 400 μg/day. It can be accelerated for pregnant women up to 600 μg/day as well as lactation 500 μg/day [8].

Alcoholics, elder people, and those who take drugs such as methotrexate and phenytoin are high risk groups in term of folate deficiency [9]. Some disease such as ulcerative colitis, Crohn's disease may alter the absorption of the folate resulting delayed healing and increased risk of oral infections [9]. Deficiency can lead in microcytic anemia (iron deficiency) or macrocytic anemia (B12 or folate deficiency) associated with some oral pathologies such as red/swollen tongue, burning of tongue/oral mucosa and angular cheilitis [9]. Folate deficiency may result in increased oxidative stress, endothelial dysfunction, genetic instability, deterioration of DNA repair, and cell apoptosis as well as periodontal disease [7]. Inadequate folate uptake or lowering of some medicines decreased folate levels in body caused by some medications, uncover some side effects, especially in oral mucosa. Folate was investigated for many aspects in dentistry especially in mucosal lesions.

2. Folate in dentistry

2.1. Folate in dental caries

Early childhood caries are identified as one or more decayed missing or filled tooth surfaces in primary dentition between 0 and 71 months. Balanced nutrition and vitamin containing consumption such as folic acid is necessary for preventing early childhood dental caries [10]. Tooth caries is the microbiological infectious disease of the teeth which results in the destruction and locally dissolution of calcified tissues. It occurs with impaired physiological balance between tooth mineral and dental plaque. Caries lesions occur when a large number of bacteria with the ability to produce acidic environments thus demineralize the tooth structure. At the onset of caries lesion, the causal relationship between caries and organisms in the mouth flora is not well understood. Calcium and phosphate ions in high concentration in saliva play an important role in remineralization.

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine and has a central role in the metabolic pathways of thiol compounds [11]. Vitamin B12, vitamin B6 and folate deficiency, which are necessary for homocysteine metabolism, can cause hyperhomocysteinemia. There is a negative correlation between serum vitamin B12, folate, vitamin B6 concentrations and plasma homocysteine concentration in healthy subjects [12]. There are many mechanisms that effect hyperhomocysteinemia, such as the induction of smooth muscle cell proliferation in the vascular intima layer, the increase in lipid accumulation in the vessel wall, the difficulty of endothelial cell breakdown, the activation of platelets and leukocytes, the increase of low density lipoprotein oxidation, the activation of platelet thromboxane synthesis, increasing oxidative stress [13, 14]. Saliva has a protective role in developing caries with its protein, hormone, antibody, antibacterial and antioxidant contents. Lower folate intake causes a rise in homocysteine levels, resulting in an increase in salivary

oxidative markers and thus an increase in caries activity [15]. In a cohort study, insufficient folate consuming in pregnancy (<6 ng/mL) increases early childhood caries in toddlers. This study defines folate deficiency as a risk factor for developing early childhood caries [16].

2.2. Folate in periodontal diseases

Periodontitis is a disease caused by specific microorganisms and causing periodontal ligament and alveolar bone loss by affecting supporting tissues of teeth [17]. Microbial dental plaque is required to start the periodontal destruction but it is not sufficient to exacerbate the periodontitis. Host inflammatory response takes an important place to modulate the disease course. Genetics, smoking, general health, diet, social variables etc. may affect the host immune response and periodontal destruction [18].

In recent years, macronutrients and micronutrients, which modulate proinflammatory and anti-inflammatory mechanisms affecting host immune response to combat with periodontitis, are gaining importance [19]. Folate takes an important place for preserving the integrity of the periodontal tissues. Gingival necrosis, periodontal ligament and alveolar bone loss can develop when the folate deficiency in body exists [20]. Folic acid deficiency reduces lymphocyte production, decreases cytotoxic T cell activity and phagocytic function of neutrophils leading the rapid development and progression of periodontal tissue destruction. High turnover of squamous epithelium process which is essential for repair of periodontal tissues is damaged when the folate levels are reduced [20].

Akpinar et al. [4] investigated effects of different B vitamins on alveolar bone loss in rats. 64 male Wistar rats were used and riboflavin, nicotinamide and folate were applied to doses 50–100 mg/kg. Serum IL-1 beta and IL-10 levels were measured by using ELISA. Alveolar bone loss, osteoclast, osteoblast number and inflammatory cell infiltration were examined histopathologically. 100 mg/kg folate group was revealed more 1 L-1 beta reduction and bone loss in all B vitamins were similar comparing the control group. They concluded that systemic administration of riboflavin, nicotinamide and folate increased osteoblast activity, decreased osteoclast numbers, and reduced alveolar bone loss in rat model.

Esaki et al. [21] studied the relationship between folate levels and gingival bleeding in 497 patients who were nonsmokers. According to the multiple regression analysis results, dietary folic acid was significantly correlated with gingival bleeding but it is not correlated with Community Periodontal Index scores.

In another rat study preventive effects of folate supplements on cyclosporine-associated bone loss; 40 male rats were divided into 5 groups. Folate were given 20 mg/kg daily via gastric gavage for 6 weeks. In cyclosporine group, mean homocysteine level was significantly higher than the other groups. Folate revealed more total mandibular volume, absolute bone volume and volume of cavities comparing with cyclosporine group [22].

Erdemir and Bergstrom [23] investigated smoking, folate and vitamin B12 levels in chronic periodontitis patients. As a result; a negative influence on the response to nonsurgical periodontal therapy in smokers and folate levels of smokers gradually decreased 8.0 ng/ml at

baseline to 7.2 ng/ml at 6 months. However, these levels increased in nonsmokers. They concluded that consuming folate and B12 rich foods provides beneficial effects for smoker periodontitis patients.

Yu et al. [7] investigated the age-related periodontal disease and folate levels in a cross sectional study, based on the data of the National Health and Nutrition Examination Survey (NHANES) 2001/02. Periodontal examination and analysis of serum folate level were performed, according to study results, low serum folate levels were correlated with periodontal disease. Authors concluded that, folate has a preventive role for development of periodontal disease and nutritional status was a messenger for oral health.

2.3. Folate in recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is an oral disease which characterized recurrent/painful ulcerations on oral mucosa such as labial, buccal, alveolar and ventral tongue (**Figure 1**). Many etiological factors such as immune disorders, hematologic diseases, hypovitaminosis, nutritional deficiencies, allergy, psychological disorders have been discussed in terms of disease etiology but exact causes of RAS remains unclear [24]. Although some studies showed that multiple nutritional deficiencies including B1, B2, B6 and B12, folate, iron and ferritin may be possible etiologies of RAS [25].

Sun et al. [25]. performed a study with 273 healthy and 273 patients with RAS. Blood iron, hemoglobin, homocysteine, B12 and folate levels were determined. RAS patients showed significantly lower mean hemoglobin and iron levels comparing the healthy subjects. In terms of mean B12, folate and homocysteine levels, RAS patients did not show any significant difference to healthy subjects.

A study was carried out with 60 patient had RAS in 6 months. Analysis was performed to determine serum ferritin and serum B12 and red blood cell (RBC) folate. RAS group had low serum folate 51.7% as well as serum ferritin, serum B12 levels in comparison, healthy subjects [26]. However, Aynali and colleagues have indicated that B12 deficiency may play a role in

Figure 1. A major aphthous stomatitis on labial mucosa.

etiology underlying RAS [27]. In their study folate and hemoglobin levels were not statistically different with that of healthy group.

Burgan et al. [28] investigated the hematinic deficiency prevalence in 286 individual (143 RAS patient and 143 control group). Hemoglobin, ferritin, vitamin B12 and folate levels were determined in serum. 54 RAS (37.8%) patient indicated low ferritin, folate or vitamin B12 compared with 26 Control (18.2%) group with a significant difference. Although male patients with RAS did not show any folate deficiency, females were deficient to folate at 9.2% rate. When hematinic deficiencies are listed, vitamin B12 (26.6%) is the first, followed by iron (16.8%) and folate (4.9%). The authors concluded that RAS can be controlled by controlling the ferritin, folate and vitamin B12 levels of patients. However Barnadas et al. concluded that replacing these elements did not make statistical difference in reducing the frequency of RAS [29]. In another study that agrees with this study, patients received daily multivitamins (including A, B1, B2, B3, B5, B6, B9, B12, C, D and E) in addition their diets showed no significant changes as for reduction in the number or duration of RAS episodes [30].

2.4. Folate in gingival hyperplasia

Gingival hyperplasia (GH) refers to the changes in gingival size and increase in gingival contour (**Figure 2**). The cause of this increase is sometimes an inflammation or sometimes an increase in gum fibrillation due to chronic irritation. Inflammatory cells reaching the inflamed area increase the size of the gingiva. As the event becomes chronic, the number of collagen fibrils in the gingiva increases and the gingival size grows. Although gingival hyperplasia is more likely to be caused by the inflammation which developed from dental plaque, some medications such as antiepileptic drugs, anticonvulsants and immunosuppressants have also been associated with GH [31]. Antiepileptic agent phenytoin, anticonvulsant agents valproic acid, carbamazepine, phenobarbital and vigabatrin, immunosuppressant cyclosporin A and calcium channel blocker dihydropyridines, diltiazem and verapamil have GH as an adverse effect [32–35]. The exact mechanisms that induce the GH have not been clearly understood, although there are a lot of studies about this topic, contradictory results remain. Some of

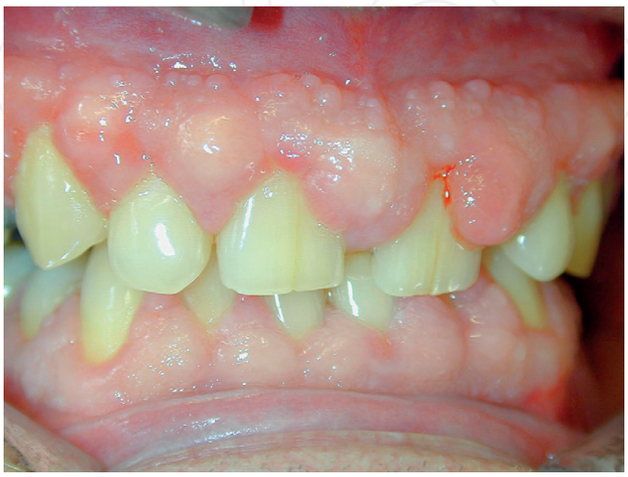

Figure 2. Typical gingival hyperplasia image.

the studies concluded that phenytoin and cyclosporine A are capable to inhibit extracellular matrix (ECM) production by gingival fibroblast and cell proliferation in vitro [36].

On the other hand, some studies indicated that the accumulation of proteins such as collagen in ECM may be caused by an imbalance between the synthesis and the degradation of ECM, became a possible explanation of the development of GH [37]. Collagen fibrils are degraded via two ways: secretion of collagenases which is named extracellular way; and the intracellular way, by collagen phagocytosis by fibroblasts [38].

Antiepileptic agents, immunosuppressants and calcium channel blockers induce a decrease in the Ca2+ cell influx by implementing differences in the sodium-calcium exchange in the result of a reduction in the uptake of folate; all these changes limit the production of active collagenase [39]. A number of studies have been conducted that point to severe folate deficiencies resulting from long-term use of phenytoin. Folate, on the other hand, were held responsible for the significant decrease in serum concentration of phenytoin, as much as to accelerate seizures [40–42] (**Figure 3**).

Vogel [43] suggested that drug induced GH may be a secondary to a local folate deficiency. Heimburger [44] noted that some tissues need greater folate for maintaining its function than other tissues which may lead to localized deficiencies, in spite of the serum folate is detected normal ranges although such localized folate deficiencies may result from reduced tissue intake due to a congenital malfunction. Opladen et al. investigated the reaction of anticonvulsant drugs on the folate receptor 1 (FOLR1)-dependent 5-methyltetrahydrofolate (MTHF) which is primary biologically active form of folate transport. The authors have dedicated reactive oxygen species (ROS) production were accelerated via metabolic cleavage caused by some anticonvulsants (valproate, carbamazepine and phenytoin). Side effect of drugs and ROS development on FOLR1-dependent 5-MTHF uptake were investigated and it was concluded that MTHF uptake was connected on the time and dosage of medication. At normal ranges of MTHF concentrations, the high-affinity FOLR1 serves the main mechanism for cellular uptake, however phenytoin increased MTHF uptake but ROS damages this physiologic condition leading to inhibition in folate transport and decrease in folate uptake in gingival fibroblasts [45].

Inoue and Harrison [46] stated that taking folate supplement with phenytoin may reduce or prevent the GH. In some studies, it was determined that recurrence of GH following surgical intervention decreased when the patient received folate [47, 48].

Based on the results obtained from various studies related to reduced plasma and tissue folate levels induced by phenytoin, folic acid was tested both topically and systemically to prevent the inevitable adverse effects of long-term phenytoin therapy [49]. However conflicting results available in literature about treatment with folate would have a therapeutic effect on phenytoin induced GH [50].

Arya et al. [51] investigated the effect of folate on phenytoin induced GH in 120 patients with epilepsy aged 6–15 years on phenytoin monotherapy for 6 months were 62 and 58, respectively, in folate and placebo arms. 0.5 mg/day of folate were given for 6 months. After 4 months, 21% of the folate arm and 83% of the placebo arm had developed phenytoin-induced GH. At

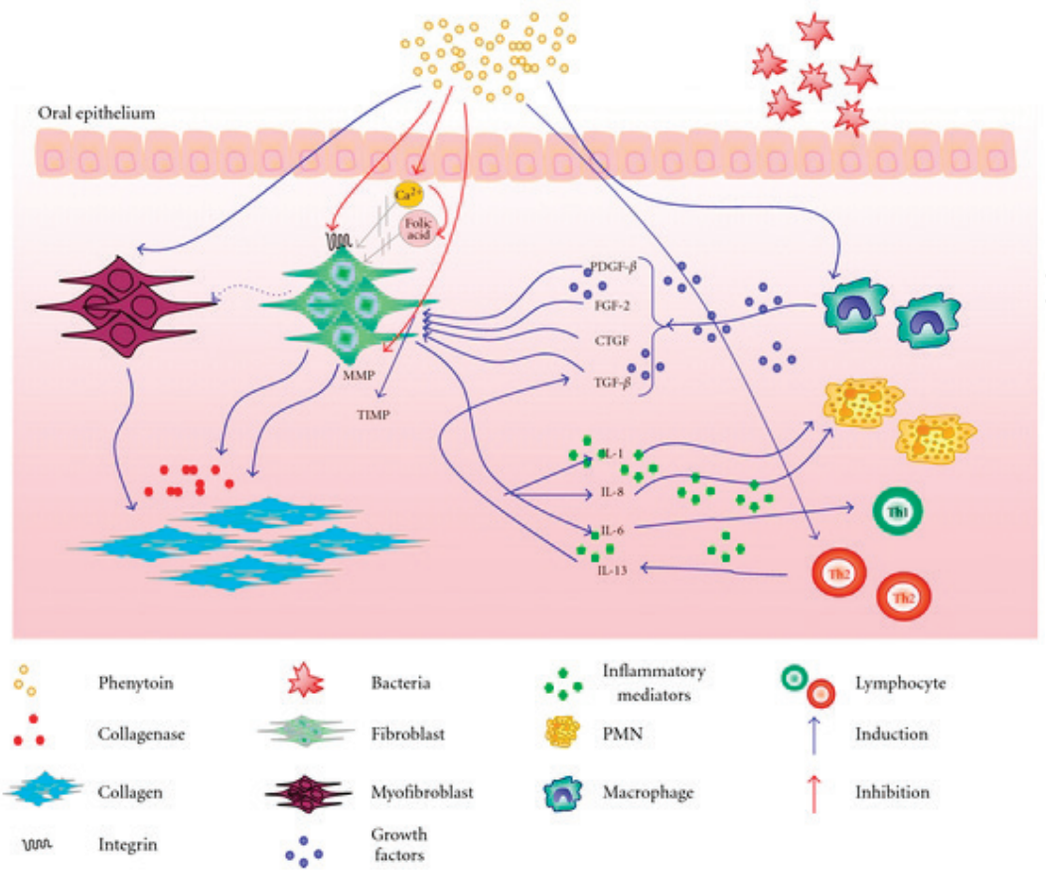

Figure 3. Mechanism of gingival hyperplasia development. Phenytoin induces a decrease in the Ca2+ cell influx that leads a reduction in the uptake of folic acid; this action limits the production of active collagenase. Phenytoin decreases collagen endocytosis via induction of a lower expression of α 2 β 1-integrin by fibroblasts and it also stimulates myofibroblasts. Cytokines is also responsible in gingival overgrowth. IL-6, IL-1, and IL-8 are produced by fibroblasts that activated by phenytoin. These mediators are responsible T cell activation and allowing the neutrophils to become active in the connective tissue. This interaction seems to be associated with fibrotic diseases at a high rate. Microbial dental plaque induce a local inflammatory response which plays important role to develop GH. CTGF, PDGF, FGF and TGF-β are growth factors which are found in fibrotic tissue and takes place in phenytoin induced GH. Th2 cell activated IL-13 production can be affected by phenytoin, furthermore; the drug may activate to macrophages releasing different growth factors such as TGF-β and CTGF. Fibroblast proliferation, collagen biosynthesis, activation of TIMPs, inhibition of MMPs and ECM synthesis which are essential to develop GH occur based on all of these biological events. PDGF-β: platelet derived growth factor; FGF-2: fibroblast growth factor-2; TGF-β: transforming growth factor-β; CTGF: connective tissue growth factor; MMP: matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase [31].

the end of the study the occurrence of phenytoin induced GH was found to be significantly decreased with folate supplementation from 88% in the control population to only 21% of those receiving folate.

In a study a total of 100 patients between the ages 18 and 50 years, who were clinically diagnosed with epilepsy treated with phenytoin participated. Assessment of serum folate level was carried out by chemiluminescent method using immulite kit at the start of and after 1 year of phenytoin therapy. The mean difference between the start and after 1 year folate level was calculated as −7.530. The authors concluded that, the use of folate as an adjuvant to phenytoin therapy in the prevention of phenytoin-induced gingival enlargement can be considered but attention is required drug interactions between the two [52].

Dogan et al. [53]. performed a study to determine the role of folate on phenytoin induced human gingival fibroblasts overgrowth by investigating its effect on IL-1beta which has been stated to accelerate the ECM production in fibroblasts induced depending tumor necrosis factor alpha (TNFalpha) in vitro. The IL-1beta level in cells in the phenytoin treated group was found 1 pg/ml. 20 or 40 ng/ml folate treated samples achieved 0.8 and 0.7 pg/ml, respectively near the control group value that was 0.7 pg/ml. Folate application decreased IL-1beta level as nearly control group. However, in the double-blind randomized controlled trial, authors compared folic supplement (3 mg/day for 16 weeks) to prevent GH. They concluded that the folate is an inadequate therapy for preventing GH [54]. Using folate (1 mg/ml mouthwash) was considered to be more effective than systemic application [48]. In one study, the authors noted that topical folate may bind to exogenous endotoxin, leading to the reduction in GH and reduce gingival inflammation. Patients who had low baseline plasma and RBC folate responded good results to topical folate than normal people [55].

2.5. Folate in birth anomalies

Neural tube defects, cleft lip, alveolar and palate are the most common malformations in humans. In spite of more advanced therapeutic measures taken in recent years, such anomalies are still being encountered and individuals born with such anomalies are exposed to severe physical and psychological difficulties.

The etiologic factors that constitute cleft lip and palate are not known exactly and are accepted as a multifactorial anomaly. In the etiology of cleft lip and palate role of both genetic and environmental factors thought to cause [56].

During the pregnancy of the mother, especially in first trimester of pregnancy exposure to chemical substances and/or the use of medicines (benzodiazepines, phenobarbital, diphenylhydantoin, diazepam, cortisone, salicylates etc.), the use of alcohol or cigarettes, infectious disease (rubella etc.), diabetes, folate deficiency, stress, exposure to radiation, inadequate or excessive vitamin A intake can affect these facial anomalies [56]. Studies that have performed during the last 20 years on the etiology of cleft lip and palate shows that there is a small but significant link between the risk of having a child with cleft lip and palate and smoking in the first 3 months of pregnancy. Researches have shown that smoking mothers have lower folate values than nonsmokers and therefore have a higher risk of having child with cleft lip and palate. It has been reported that alcohol use during pregnancy also increases the risk of developing cleft lip and palate [56–59].

Most of the face development occurs at 4–8 weeks in pregnancy. At the end of the 10th week a clear face appearance emerges. In the process of facial development, medial nasal processes, lateral nasal processes and maxillary processes combine to form the normal nose, upper palate and lip anatomy. The result of the combination of the medial nasal and maxillary process, oral and nasal cavities are separated. The mandibular process forms the lower jaw, lower lip and lower part of the cheek. The junctions of facial processes are weak and they are affected very quickly from any pause in this phase. Development and merging inability of these processes result in lip or palatal clefts [60].

The classification used today is the Kernahan classification based on the embryonic formation theory. In this class, the limit used for separating deformities is foramen incisivum. The structures in front (premaxilla and nose) are called "primary palate" and the structures behind it (hard and soft palate) are called "secondary palate." Accordingly, Kernahan has divided the lip and palate cleft into three main groups: 1. Only primer palate (lip and premaxilla) clefts 2. Only the secondary palate clefts 3. Co-clefts of primer and secondary palate [61] (**Figure 4**). With a simple classification, oral clefts can be separated into two main categories: cleft palate only and cleft lip with or without cleft palate. Causal mechanisms of these categories may be different. Most of the clefts are defined as isolated, which means that there are no accompanying birth defects (**Figure 5**). In non-isolated clefts different severe anomalies may develop, congenital heart defects and neural tube defects are more frequently accompany with oral clefts [62].

Oral cleft defects are the most frequent newborn defects that can be observed 1/500 approximately in worldwide which are related to folate deficiency. Palatal and lip clefts are responsible for these oral clefts [63]. Oral cleft occurrence in early life period is an important health problem in which different surgical procedures must be frequently performed. Also dental treatment, physiological support, speech correction are the secondary common problems [64]. In an animal study on the relationship between folic acid and cleft lip and palate, more cleft lip and palate was found in animals fed with folate deficient diet. In another study in which folic acid supplementation was given to pregnant mothers using anticonvulsant medication, none of the 33 mothers who received folic acid supplementation were reported to have cleft lip and palate and/or developmental defects [59]. Although the mechanism of action of folic acid is not fully understood, it is suggested that women who are planning to have children in order to prevent cleft lip and palate and neural tube defects present with 0.4 mg of folic acid daily before the 12th week of pregnancy and before getting pregnant [58, 59, 65]. Folic acid and reducing risk for neural tube defects is well recognized. Facial and tooth tissues develop from neural crest cells which originate from the dorsolateral aspect of the developing neural tube thus neural tube defects and oral clefts are embryologically related to each other [66]. Folate is also an important vitamin which is required for synthesis of DNA and RNA. There is a wide investigation about maternal consumption of vitamins and especially folate that reduces oral cleft recurrence and occurrence [67]. Both 0.4 and 4 mg doses of folate intake significantly reduced oral cleft prevalence during pregnancy may play an important role on preventing oral clefts [64, 67]. In contrast, a population based study revealed that supplementary

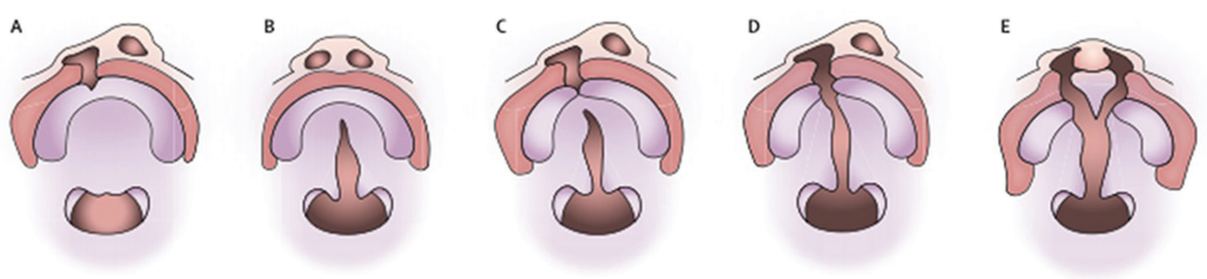

Figure 4. (A) Cleft lip and alveolus. (B) Cleft palate. (C) Incomplete unilateral cleft lip and palate. (D) Complete unilateral cleft lip and palate. (E) Complete bilateral cleft lip and palate [63].

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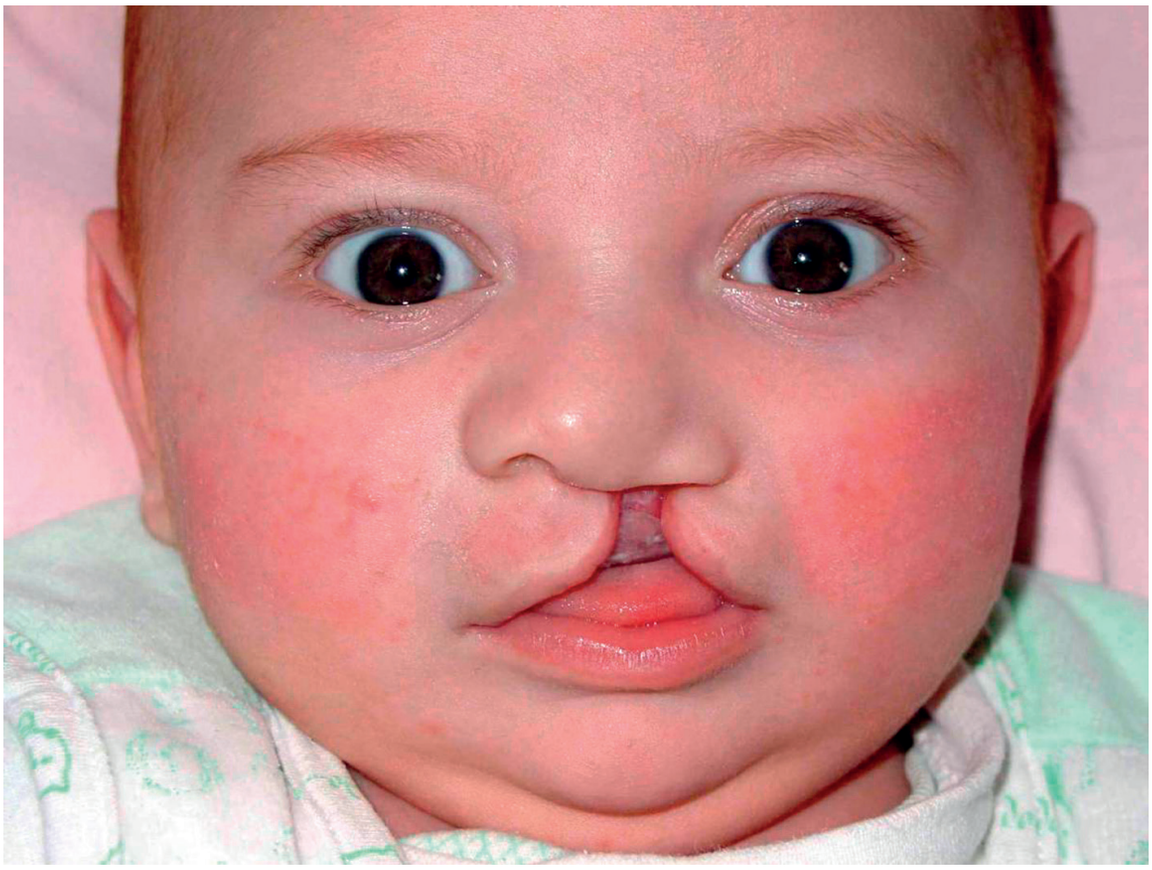

Figure 5. A baby born with cleft lip and palate.

folate intake has no effect on the prevalence of oral clefts [62]. In another recent study folate intake 4.36 fold reduced palatal and lip or combined clefts when used in early pregnancy (4–12 weeks) 400 μg daily [68]. In a population-based study 896,674 live births which 1623 had oral clefts (isolated oral clefts, *n* 1311; non-isolated oral clefts, *n* 312) were investigated. 21.5% women used vitamin supplements before getting pregnant. Vitamin use provided no additional benefit to prevent the isolated oral clefts [62].

2.6. Folate in cancers

Folate is necessary for maintaining proper body functions also for the preservation of genomic integrity. Folate joins in two groups of biological reactions, one of them is biosynthesis of nucleotides and the other is methylation reactions. These events are required in the basic biological mechanism of DNA synthesis, repair and methylation. Also it is needed for mitochondria to function correctly and preservation of mitochondrial DNA. Specifically, DNA damage caused by the deficiency of folate may result in the formation of chromosomal abnormalities, these abnormalities are considered as one of the main results of cancer and leukemia [69].

Folate deficiency in rats has demonstrated increased sensitivity to carcinogenicity. Although the mechanism of anticarcinogenic action of folate is not fully known, it is thought to be related to DNA methylation. It is thought that folate can decrease carcinogenesis because of

its role in the maintenance of the level of SAM (S-adenosylmethionine) and the production of deoxythymidine monophosphate necessary for DNA synthesis. In the case of hypomethylation in cytosine-guanine chains, the expression of specific oncogenes may increase. It has been reported that defective or incomplete methylation DNA associated with dietary folate deficiency can develop a mechanism to cause cancer and aging [70].

There are recommendations about that folate intake may decrease oral cavity and pharyngeal cancers (OPC). Therefore many studies have limited sample size and the common problem is the main source of dietary folate [71]. OPC is seventh most common cancer worldwide. Tobacco and alcohol may be identified as the main risk factors for OPC; additionally, dietary risk factors are also responsible for OPC. Fruit and vegetable rich diet which highly include folate can reduce risk of OPC, [72, 73]. Recently authors have found that folate intake may significantly reduce overall OPC risk. Folate intake by consumption revealed weaker association between OPC risks. Using alcohol increased risk of OPC about 11% when compared to never/light drinkers [71]. In another study significant difference was found according to aldehyde dehydrogenase 2 gene polymorphism that related to alcohol consumption. Also folate intake has reduced OPC risk in this patients [74]. Interestingly authors stated that dietary folate intake may contribute to the proliferation in early-stage colon cancer. Folate is strongly related to DNA and RNA replication and tumor suppressor gene expression. It is recommended that daily 400 micrograms of folate is necessary for the homeostasis. Also HPV is responsible for initiating OPC, and folate has an important role in suppressing carcinogenic cell production via mediating methyl groups for CpG-specific DNA methylation [75]. Using alcohol reduces gastrointestinal absorption of folate, and it has been shown that high alcohol intake causes a higher acetaldehyde plasma concentration resulting reduced folate plasma levels [76]. In a more recent study folate-alcohol intake association in women's oral cancer revealed that high alcohol intake with low folate intake increases cancer risk. Also high alcohol intake with higher folate intake decreases the risk [77]. Alcohol dehydrogenase and cytochrome P450 2E1 enzymes convert ethanol to acetaldehyde which plays key role on cariogenic effect of alcohol. Acetaldehyde has effects on DNA methylation and DNA repair systems [78]. It is hypothesized that increased levels of aldehyde dehydrogenase 1 enzyme also increases acetate concentrations which is an end product of acetaldehyde. So acetaldehyde concentration which has a negative effect on folate metabolism reduces. We can conclude that acetaldehyde may play an important role as a key factor in OPC. At this point we can explain how the carcinogenic effect of alcohol reacts on human body. As a result people who drink high alcohol and oppositely have low folate intake are in the most risky class [79].

3. Conclusion

Socioeconomic factors are the most important factors leading to nutritional disorders. Folate deficiency prevents the organism from maintaining its important metabolic activities and causes various disorders. Especially to participate in DNA synthesis, in the early stages of pregnancy and the baby is very important for the development of children to adolescence. Among the daily diet of constantly consumed nutrients folate content is very important in

terms of combating folate deficiency. We have to be vigilant and take into consideration as an etiological factor the clinical table which develops from the deficiency of these vitamins. Controlled studies have shown that the use of periconceptional folate reduces the frequency of urinary system, cardiovascular and extremity anomalies, as well as the frequency of cleft lip and palate [80]. In addition, correction of the folate status of the person reduces vascular diseases and the incidences of certain cancers [81]. Taking all of these into consideration, for the primary protection of various diseases, enrichment of foods with folate, promotion of the use of folate tablets by risky people and education of consumption of foods rich in folate should be considered.

Author details

Aysan Lektemur Alpan[1]* and Nebi Cansin Karakan[2]

*Address all correspondence to: ysnlpn@gmail.com

1 Department of Periodontology, Faculty of Dentistry, Pamukkale University, Denizli, Turkey

2 Department of Periodontology, Faculty of Dentistry, Afyon Kocatepe University, Afyonkarahisar, Turkey

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