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# ZNAČAJ MIKRONUTRIJENATA U USNOJ DUPLJI

# IMPORTANCE OF MICRONUTRIENTS IN THE ORAL CAVITY

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***Sažetak***

***Uvod:****Mikronutrijenti igraju moćnu ulogu u funkcionisanju različitih sistema organizma. Za održanje optimalnog stanja usne duplje neophodno je održati adekvatan status mikronutrijenata.*
***Cilj:*** *Istaći značaj različitih mikronutritijenata za normalno funkcionisanje usne duplje, kao i njihov uticaj na pojavu različitih oboljenja mekih i tvrdih tkiva usne duplje.*
***Zaključak:*** *Mikronutrijentikaoštosu vitamin C, B9 i E, kalcijum, cink, bakar i gvožđe imaju osim gradivnih i anti inflamatorna svojstva i deluju kao antioksidansi. Nedostatak određenih mikronutrijenata ima važnu ulogu u razvoju parodontopatije i karijesa. Osobe sa hroničnim inflamatornim oboljenjem creva, kao i deca,trudnice i dojilje obično su deficitarni u ovim vitaminima i zato često podložni razvoju inflamatornih promena na mekim tkivim usne duplje, nastanku parodontopatije i karijesa.*

***Ključne reči:*** *malnutricija, antioksidans, inflamacija, parodontopatija, karijes*

***Abstract***

***Introduction:*** *Micronutrients play a potent role in the functioning of the different systems of the organism. It is necessary to sustain an adequate status of the micronutrients for maintaining the optimal condition of the oral cavity.*
***The aim:*** *Toemphasize the importance of different micronutrients for the normal functioning of the oral cavity, as well as their influence on the occurrence of various diseases of the soft and hard tissues of the oral cavity.*
***Conclusion:*** *Micronutrients such as vitamin C, B9 and E, calcium, zinc, copper and iron have a role in development so as anti-inflammatory and antioxidants properties Deficiency of certain micronutrients plays an important role in the development of periodontitis and caries. People with chronic inflammatory bowel disease, as well as children, pregnant and breastfeeding women, are usually deficient in these vitamins and therefore often susceptible to the development of inflammatory changes in soft tissues of oral cavity , periodontitis and caries.*

***Key words:*** *malnutrition, antioxidant, inflammation, periodontitis, caries*

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## *Uvod*

Dovoljna količina mikronutrijenata od ključnog je značaja za zdravo oralno okruženje. Na primer, brzi imuni odgovor značajan je ukoliko postoji zapaljenski proces. To je moguće obezbediti ukoliko je telo snabdeveno odgovarajućom ishranom[1]. In vitro studijama je pokazano da vitamini i supstance u tragovima imaju značajnu ulogu u svim aspektima imunološke funkcije i da njihov deficit može narušiti imunološku funkciju[2]. Konzumiranje dovoljne količine proteina i amino-kiselina može sprečiti različita oboljenja usne duplje, s obzirom na to da njihova deficijencija može dovesti do disfunkcije pljuvačnih žlezdi[3], promeniti antibakterijska svojstva pljuvačke I promeniti sposobnost zaceljenja mekih oralnih tkiva[4]. Zapravo, pljuvačka se može koristiti i kao medijum za praćenje rizika za nastanak karijsa[5]. Drugu sličnu patologiju čine oboljenja parodoncijuma, kao što su gingivitis i parodontopatija, koja imaju sličan trend progresije. Osim toga, mikronutrijenti deluju kao katalizatori metaboličkih reakcija. Budući da se samo malo vrsta hrane zapravo sastoji iz mikronutrijenata, od krucijalnog je značaja održati njihov balans, što se često postiže dodavanjem suplemenata[6]. Drugi zanemareni problemi su emocionalne i psihološke smetnje povezane sa kvalitetom života osoba sa oboljenjima usne duplje[7,8].

I pored značajnih uloga mikronitrijenata, veliki deo populacije je u njihovom deficitu. Na primer, Svetska zdravstvena organizacija (SZO) identifikovala je to da su u mnogim zemljama regiona Srednjeg Istoka, naročito deca i žene u reproduktivnom periodu deficitarni u kalcijumu, gvožđu, cinku, vitaminima A i D, i folatima[9]. Slično, statistika pokazuje to da je oko 33% ljudi, uglavnom žena, deficitarno u gvožđu. Nadalje, 13,2 milona predškolske dece ima nivo serumskog retinola ispod 0,7 μmol/L, i znatno niže od toga, te da oko 800 000 ljudi pati od noćnog slepila[9].

U cilju poboljšanja kvaliteta života, trebalo bi dobro proceniti unos[10] ugljenih hidrata, proteina i mikronutrijenata naročito kod dece[11]. Međutim, treba naglasiti to da se uprkos dobro izbalansiranoj ishrani, može desti da pojedinac i dalje ne unese preporučene dnevne doze mikronutrijenata. Pored nedovoljnog unosa usled nepravilne ishrane, do deficijencije može doći i usled poremećaja u apsorpciji, interakcije sa lekovima, drugih hroničnih oboljenja[12,13]. Pored inherentnog rizika od deficijentnog stanja, dugoročne posledice smanjenog unosa vitamina i elemenata mogu se odraziti na fiziološke funkcije, mogu dovesti do ćelijske neispravnosti i povećanja rizika od nastanka hroničnih oboljenja[13-15].

## *Introduction*

Sufficient supply of micronutrients is thekey to having a healthy oral environment. For instance, a quick immune response is important if there is an inflammatory process. This is possible provided that the body is supplied with proper nutrition[1]. It has been proved in-vitro that vitamins and trace components play an important role in all aspects of immune function and their deficiency can lead to impaired immune function[2]. Consuming enough amounts of proteins and amino acids can prevent different diseases of the oral cavity because deficiency of them can lead to dysfunction of salivary glands[3], change in an antibacterial property of saliva and wound healing capacity of soft oral tissue[4]. Indeed, saliva can be used as monitoring medium for determining the risk for caries development[5]. Other similar pathologies are diseases of the periodontium, like gingivitis and periodontitis, which have a similar course of progression. Furthermore, micronutrients act as a catalyst for all metabolic reactions. Sinceonly a small amount of food actually consists of micronutrients, it is crucial to maintain its balance, sometimes by administering food supplements[6]. Other underestimated problems are the emotional and psychological distraught associated with the quality of life due to the oral damage[7,8].

Despite the important functions of the micronutrients, a big chunk of population is lacking them. For example, WHO has identified that in many countries in the Middle East region, especially children and women of reproductive age to be deficient in calcium, iron, zinc, vitamin A, vitamin D and folate[9]. Similarly, statistics show that about 33% of people, the majority of whom are women, lack iron. Furthermore, 13.2 million preschool children have their retinol serum level below 0.7 μmol/L, and even worse, about 800.000 of them are suffering from night blindness[9].

In order to improve the quality of life, the nourishment in the form of carbohydrate, proteins and micronutrients should be well assessed[10], especially in thecase of children[11]. But it is to be noted that, despite a properlybalanced diet, an individual can still fall short of meeting recommended micronutrient allowances. In addition to insufficient micronutrient intakes due to poor diet, deficiencies can still be a problem due to inherent risk for deficiency states, the long-term consequence of decreased intake of vitamins and elements can be linked with physiological performance,cellularmalfunction and increased risk for chronic disease[13-15].

***Efekti mikronutrijenata u usnoj duplji***

***Efekti makroelemenata i elemenata u tragovima***

***Magnezijum***

Postoje dokazi da deficit megnezijuma povećava rizik od pojave parodontopatija. Netretirana parodontopatija takođe može usloviti probleme na drugim organima organizma. Analiza zasnovana na populacionoj studiji pokazala je to da dodatak magnezijuma u vidu suplemenata može poboljšati zdravlje parodoncijuma, redukujući gubitak periodontalnog pripoja[17]. Slično, magnezijum pomaže u aktiviranju vitamina D, koji za uzvrat reguliše homeostazu kalcijuma i fosfata koji utiču narast o održanje kostiju. Na sličan način, magnezijum utiče na stabilnost ćelijske funkcije, sintezu RNK i DNK, ćelijski oksidacioni status i ćelijsku reparaciju. Takođe, magnezijum ima značajnu ulogu u aktivaciji značajnih transporta i enzima[18] i smatra se da je njegova deficijencija okidač za apoptozu[19]. Slično ovome, studije pokazuju to da postoji međuzavisni odnos između konzumiranja magnezijuma i karijesa[20].

***Kalcijum***

Sledeći značajan element je kalcijum. Prema podacima trećeg Nacionalnog ispitivanja zdravstvenog stanja i ishrane (NIZSI III), nizak unos kalcijuma može rezultirati težom formom parodontalnog oboljenja, a takođe može uticati i na gustinu minerala i jačinu potpornih struktura zuba[21]. Prema studiji sprovedenoj u SAD na civilnoj neinstitucionalizovanoj populaciji, povezanost niskog unosa kalcijuma sa parodontalnim oboljenjem najčešće je pronađena kod mladih muškaraca i žena (starosti 20 do 39 godina) i starijih muškaraca (starosti 40 do 59 godina)[22]. Druga povezanost ogleda se između niskog nivoa kalcijuma i visokog nivoa fosfata u krvi nastalog usled neadekvatne niske koncentracije parathormona (PTH). Regularan tretman hipoparatireodizma može uključiti aktivirani vitamin D i/ili kalcijum suplemetaciju, ali ova terapija ne može u potpunosti zameniti funkciju PTH i može usloviti kratkotrajne probleme (kao što su hipoklacijemija, hiperkalcijemija i povećano izlučivanje kalcijuma putem urinarnog trakta), te je zamena PTH prikazana kao nova opcija lečenja[23]. S druge strane, primarni hipoparatireoidizam može povećati nivo kalcijuma u serumu sa neprimereno nesupresioniranim niovoom PTH. Hiper-kacijemija, koja se razvija kao rezultat

***Effects of micronutrients in the oral cavity***

***Effects of macro and trace elements***

***Magnesium***

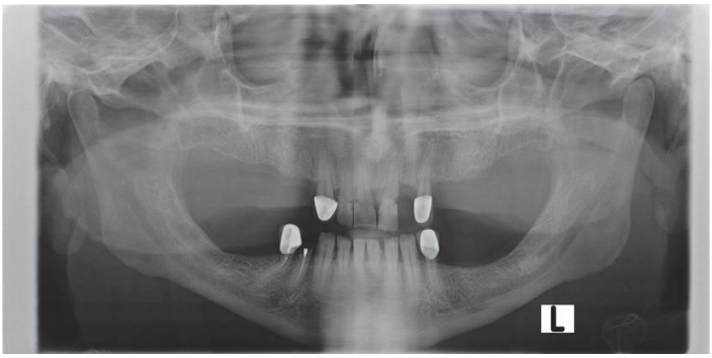
There is a piece of evidence that magnesium deficiency increases the risks for the development of periodontitis. Periodontitis, if untreated, can cause health problems in other parts of the body as well[16]. A population-based analysis revealed that nutritional magnesium supplementation may improve periodontal health, reducing periodontal attachment loss[17]. Similarly, magnesium helps in activating vitamin D, which in turn regulates calcium and phosphate homeostasis to influence bone growth and maintenance. In the same way, stability of cell function, RNA and DNA synthesis, cell's oxidation status and cell repairs are performed by magnesium. It has also a vital role in activating important transports and enzymes[18], and it has been suspected that its deficiency can trigger apoptosis[19]. Similarly, studies show that there is an intricate link between magnesium consumption and dental caries[20].

***Calcium***

The next important element is calcium. According to data from the third National Health and Nutrition Examination Survey (NHANES III), low dietary intake of calcium may result in more severe periodontal disease as well as affect bone mineral density and strength to anchor tooth structure[21]. According to a study in U.S. civilian non-institutionalized population, the relation of lower dietary calcium intake with periodontal disease was found more often in young males and females (20 to 39 years of age), and in older males (40 to 59 years of age)[22]. Another assessable issue is low calcium levels and high phosphate levels in the blood due to inadequate low concentrations of parathyroid hormone (PTH). Regular treatment for hypoparathyroidism may include activated vitamin D and/or calcium supplements, but this treatment may not fully replace the functions of of PTH and can lead to short-term problems (such as hypocalcaemia, hypercalcaemia and increased urinary calcium excretion), so PTH replacement has been demonstrated as a new treatment option[23]. On the other hand, primary hyperparathyroidism may elevate serum calcium level with an inappropriately non suppressed PTH level. The hypercalcemia that develops as a result of primary hyperparathyroidism leads to osteoporosis (Picture 1), nephrolithiasis,

primernog hiperparatieroidizma, dovodi do pojave osteoporoze (Slika 1), nefrolitijaze, pankreatitisa i neurokognitivnih deficita kao što su poteškoće sa memorijom, koncentracijom i spavanjem[24]. Morfometrijske analize pokazuju to da je slučajna primena PTH (40 μg/kg) uspela da zaštiti zub od koštane resorpcije izazvane parodontopatijom. Prema studiji sprovedenoj u Kini, uočen je potencijal intermitentnog PTH da stimuliše cementogenezu. Intermitentni PTH ograničio je inhibiciju cementogeneze i diferen-cijacije cementoblasta. Oba ova nalaza sugerišu to da se intemitentni PTH može terapijski koristiti za poboljšanje prognoze resorpcije korena zuba[25].

pancreatitis, and neurocognitive deficits such as difficulty with memory, concentration and sleep[24]. The morphometric analysis demonstrates that random PTH administration (40 μg/kg) was able to protect the tooth site from periodontitis-induced bone resorption. According to a study conducted in China, the potential of intermittent PTH to promote cementogenesis was observed. Intermittent PTH restrained the inhibition of cementogenesis and cementoblast dif-ferentiation by a mechanical strain. Taken together, these findings suggest that intermittent PTH can be therapeutically exploited to improve the prognosis of tooth root resorption[25].



***Slika 1.*** Osteoporoza se uočava kao razređenje kostiju i proređivanje korteksa[26]
***Picture 1.*** Osteoporosis seen as rarefying of the bone and thinning of the cortex[26]

### *Gvožđe*

Gvožđe deficitarna anemija uključuje atrofiju jezičnih papila, peckanje i crvenilo jezika, angularni stomatitis, disfagiju, bledilo oralnih tkiva nastalog usled anemije[22]. Plummer-Vinsonov sindrom(Slika 2) je genetsko stanje povezano sa deficitom gvožđa, i manifestuje se angularnim stomatitom, glositisom i disfagijom[28].

### *Iron*

Iron deficiency anaemia includes atrophy of the lingual papillae, burning and redness of the tongue, angular stomatitis, dysphagia, and the pallor of the oral tissues due to underlying anaemia[27]. Plummer-Vinson syndrome (Picture 2) is a genetic condition related to the deficiency of iron and presents with angular stomatitis, glossitis, and dysphagia[28].

***Slika 2.*** Slučaj Plummer-Vinsonovog sindroma pokazuje angularni heilitis i gladak jezik sa gubitkom normalnih papilla jezika[29]
***Picture 2.*** A case of Plummer-Vinson syndrome showing angular cheilitis and smooth tongue with loss of the normal tongue papillae[29]

### *Cink i bakar*

Deficit cinka može dovesti do promena u epitelu jezika, povećanja broja ćelija, poravnanja filiformnih papila, pojave ulceracija i kserostomije[27]. Cink poboljšava čulo ukusa i apetit; stoga deficit cinka može smanjiti čulo ukusa, što može biti povezano sa problemom malnutricije[25]. Takođe smatra se da se može dovesti u vezu sa karijesom[31]. Cink takođe može da obezbediti zarastanje rane[32] tako što učestvuje u svakoj fazi procesa zarastanja rane od reparacije membrane, koagulacije, angiogeneze, oksidativnog stresa, inflamacije imunološke odbrane, do formiranja fibroze[33]. S druge strane apsorpcija bakra je direktno proporcionalna koncentraciji cinka[34]. Postoji nekoliko dokaza da nedostatak bakra može povećati rizik od pojave karijesa. U studiji, koja je obuhvatila 60 pacijenata, uzrasta od 3 godine do 15 godina, pacijenti su bili podeljeni u dve grupe, grupu dece sa aktivnim karijesom i drugugrupu dece bez karijesa. Zapaženo je da deca bez karijesa imaju viši nivo bakra[35]. Na glodarima je pokazano to da bakar inhibira enzime koji sadrže S-H, što može otežati proizvodnju kiselina u dentalnom plaku i stvaranje karijesa[31]. Deficit cinka i bakra povećava rizik od pojave infektivnih stanja[37].

Štaviše, nedostatak cinka može potisnuti antiinflamatorni i imunološki odgovor mekih tkiva usne duplje[21].

### *Selen*

Studija sprovedena u Finskoj, gde je nedostatak selena široko rasprostranjen, pokazala je to da dodatak ovog ultra-mikroelementa ima sposobnost smanjenja karijesa kod mladih Finaca, jer je kolagen najvažnija komponenta organskog matriksa zuba, a selen može da zameni sumpor u vezama kolagena i smanjuje zubni karijes[39].

### *Fluor*

Fluor sprečava pojavu karijesa[39] uglavnom svojim lokalnim dejstvom. Tokom izloženosti kiselinama fluoridi se apsorbuju za površinu kristala hidroksiapaptita inhibirajući demineralizaciju (Figura 1(a), Fugura 1(b)). Kada se pH ponovo uspostavi , mala količina fluorida u rastvoru učiniće rastvor visokoprezasićenim, povećavajući proces remine-ralizacije. Na sličan način, mineral koji nastaje pod dejstvom nukleacije delimično rastvorenih minerala preferencijalno će sadržati fluor i uzimaće karbonat, čineći gleđ otpornijom na buduće kisele izazove[40]. Osim toga, osim sprečavanja nastanka sekundarnog karijesa, fluor deluje i antimikrobno[41]. Stoga,

### *Zinc and Copper*

Deficiency of zinc may cause changes to the epithelium of the tongue, increase cell numbers, flatten filiform papillae, cause ulcers and xerostomia[27]. Zinc can improve taste and appetite; thus, deficiency of zinc also may cause a decrease in taste sensation, which can be related to the malnutrition problem[30]. It is also considered to be associated with dental caries[31]. Zinc also can promote the healing of wounds[32] by taking part in each phase of the wound healing process, ranging from membrane repair, coagulation, angiogenesis, oxidative stress, inflammation and immune defence, to fibrosis formation[33]. On the other hand, the absorption of copper is inverselyproportional to the concentration of zinc[34]. There is a shred of evidence that the lack of copper can increase the risks of caries. In the study conducted on 60 patients aged 3-15 years, patients were divided into two groups: one with active caries and the other without caries. The observation showed that thecaries-free group had a higher level of copper[35]. It has been shown to inhibit S-H containing enzymes on rodents, which may impede acid production in dental plaque and caries[36]. Deficiency of zinc and copper increases the risk of infectious diseases[37]. Moreover, zinc deficiency can depress anti-inflammatory and immune response of oral soft tissue[21].

### *Selenium*

A study conducted in Finland, where selenium deficiency is widespread, demonstrated that thesupplementation of this ultra-trace element has the capability to reduce caries in young Finns since collagen is the most important component of the organic matrix of the teeth and selenium can replace sulphur in bonds of collagen and reduce dental caries[39].

### *Fluorine*

Fluorine prevents tooth decay[39] mainly by its topical effect. During the acidic challenge, fluorideis absorbed to the surface of the apatite crystals which inhibits demineralization (Fig. 1(a), 1(b)). When the pH is re-established, a small amount of fluoride in solution will make it highly supersaturated in comparison fluor-hydroxyapatite, increasing the process of remineralization. Similarly, the mineral formed under the nucleating action of the partially dissolved minerals will then preferentially include fluoride and exclude carbonate, rendering the enamel more resistant to future acidic challenges[40].

stomatolozi koriste fluoride u lečenju karijesa[42].

Istovremeno, treba da budemo svesni toksičnih efekata fluoride, koji mogu dovesti do pojave fleka na zubima od blagih, bele boje (Slika 3), do ekstremno izraženih, braonkaste prebojenosti i doprineti formiranju rupica u gleđi[36]. Kao što je pomenuto , nedostatak fluorida može dovesti do povećanja zubnog karijesa, ali ne utiče na sluzokožu.

Moreover, besides preventing secondary caries[41], it also has an antimicrobial action. So dental professionals use fluorides in caries management[42].

At the same time, we should be aware of toxic effects of fluorides that can lead to mottling of the enamel ranging from mild white flecks (Picture 3) to extreme brown discoloration and enamel pitting[43]. As mentioned, deficiency of fluorides can lead to increase indental caries but it does not affect mucous membranes.

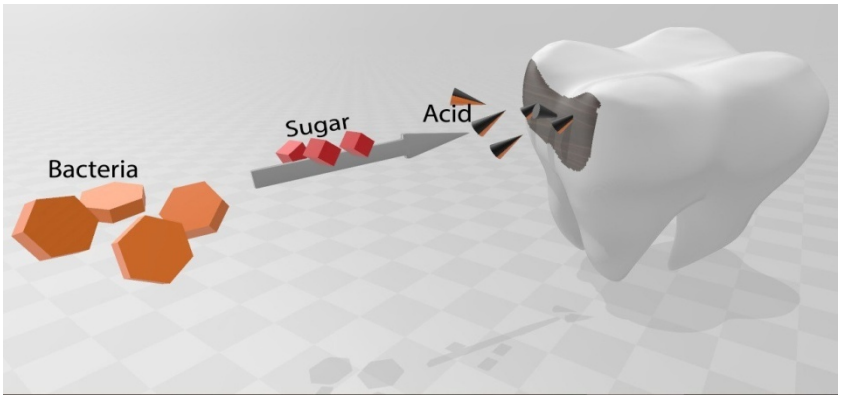



***Figura 1* (a).** Kiselina, prodire u običan sloj hidroksiapaptita ($Ca_{10}(PO_4)_6(OH)_2$), uslovljavajući pojavu karijesa

***Figure 1* (a).** Acid, penetrating the usual layer of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), eventually leading to caries

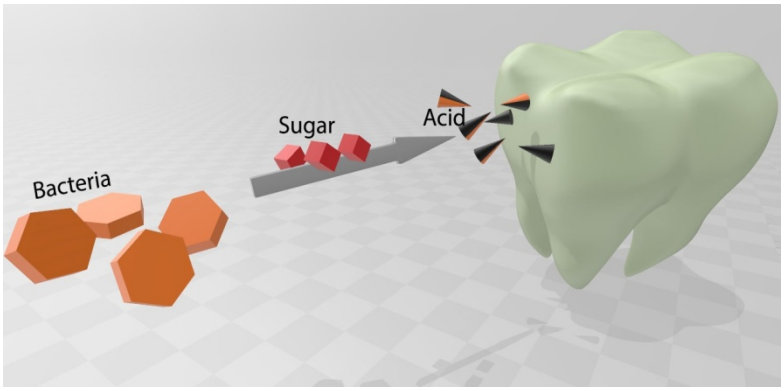



***Figura 1* (b).** Kiselina, nesposobna da prodre u film fluorapatita ($Ca_{10}(PO_4)_6F_2$), što na prvom mestu sprečava formiranje karijesa

***Figure 1* (b).** Acid, unable to penetrate the film of fluorapatite ($Ca_{10}(PO_4)_6F_2$), preventing the formation of caries in the first place

***Slika 3***. Bele mrlje kao rezultat prekomernog unosa fluorida[44]
***Picture 3***. White flecks as a result of fluorine overdose[44]

### *Efekti vitamina*
### *Folna kiselina*

Deficit folne kiseline je učestala pojava. Prema Vogelu i sar. deficit folne kiseline povezuje se sa teškom formom inflamacije gingive[45]. Osim toga, epitelne ćelije ne mogu efikasno da se dele bez folne kiseline[46]. Iako povezanost između folne kiseline i formiranja i razvoja parodontalnih džepova još uvek nije dovoljno jasna, prema nekim studijama upotreba folne kiseline može biti od značaja za prevenciju inflamacije gingive[47] i patoloških promena na jeziku koje su vezi sa time kao što su poremećaj govora i mastikacije[48]. Folna kiselina takođe može redukovati patološke promene na jeziku kao što su glositis i papilarna atrofija[49]. Prema Esakiju i sar., povezanost upotrebe folne kiseline i krvarenja gingive u grupi nepušača u Japanu pokazala je da upotreba folne kiseline može biti značajan indikator krvarenja gingive kod odraslih osoba i može obezbediti promociju zdravlja gingive[50].

### *Vitamin $B_{12}$*

Kohortna studija koju su sproveli Zong i sar., pokazala je to da je serumski vitamin $B_{12}$ obrnuto povezan sa progresijom parodontalnog oboljenja i gubitkom zuba[51]. Druga studija preseka sprovedena na deci uzrasta od 10 do 14 godina pokazala je to da sistemski deficit vitamina $B_{12}$ je bio glavni krivac porasta karijesa zuba kod dece i istaknuta je povezanost sa gingivalnim problemima kod ove dece[52]. Slično ovome, deficit vitamina $B_{12}$ odgovoran je i za pojavu glositisa, kao i atrofiju filiformnih papila[21].

### *Vitamin C*

Vitamin C takođe ima značajnu ulogu u protekciji parodontalnih tkiva (Slika 4). Amaliya i sar. pronašli su negativnu povezanost nivoa askorbata u plazmi i oštećenja parodonta[53].

### *Effects of vitamins*
### *Folic acid*

Deficiency of folic acid is a common issue. According to Vogel et al., folic acid deficiency is related to severe gingival inflammation[45]. Besides it, epithelial cells do not divide properly without folic acid[46]. Although the relation among folic acid, the periodontal pocket formation and development is not quite understood, according to some studies, use of folic acid could be important for the prevention of gingival inflammation[47] and pathologies related to it, like impeded speech or mastication[48]. Folic acid can also reduce pathologies of the tongue like glossitis and papillary atrophy[21]. A healthy gingiva maintains a healthy periodontal condition[49]. According to Esaki et al., a correlation between intake of folate and gingival bleeding in the non-smoking group in Japan revealed that intake of folic acid could be an important indicator of gingival bleeding in adults and may provide a lead to promote gingival health[50].

### *Vitamin $B_{12}$*

In a cohort study conducted by Zong et al., it was revealed that serum vitamin $B_{12}$ was inversely associated with periodontal progression and risk of tooth loss[51]. In another cross-sectional study done on children from 10 to 14 years old, it was found that systemic vitamin $B_{12}$ deficiency was the main culprit which increased dental caries and associated gingival problems in those children[52]. Similarly, lack of vitamin $B_{12}$ is also responsible for glossitis and filiform papillary atrophy[21].

### *Vitamin C*

Vitamin C may also play a significant role in the protection of periodontal tissues (Picture 4). Amaliya et al. have found a negative correlation between plasma ascorbate levels and periodontal breakdown[53].

***Slika 4(a).*** Slika parodontalnog tkiva slikana pre davanja askorbinske kiseline. Uočava se rekurentno urastanje gingive nakon druge gingivektomije i pre davanja askorbinske kiseline. Bela polja ukazuju na tipična mesta rekurentnog gingivalnog urastanja[55]

***Picture 4(a).*** Periodontal images taken before ascorbic acid supplementation. Recurrent gingival overgrowth observed after the second gingivectomy and before ascorbic acid supplementation. The white arrows indicate typical sites of recurrent gingival overgrowth[55]

***Slika 4 (b).*** Slika parodontalnog tkiva slikanja 9 meseci nakon uzimanja askorbinske kiseline[55]

***Picture 4 (b):*** Periodontal images taken after 9 months of ascorbic acid supplementation[55]

Paillaud i sar. pružili su drugi dokaz o povećanom riziku od nastanka parodontalnih oboljenja usled deficita vitamina C[54]. Osim toga, pronađeno je to da blagi deficit vitamina C je povezan sa obimnim urastanjem gingive u prisustvu metaboličkog sindroma i teške parodontalne infekcije[55]. Kao dodatak ovome, autori su pokazali i povezanost deficijencije vitamin C sa gingivitisom, ulceracijama u usnoj duplji, i nekoliko abnormalnosti gingive (sunđerasta gingiva, krvarenje, izrazito crvena gingiva)[21,53]. Deficit vitamina C takođe može biti značajan nezavisni faktor rizika od pojave oralne kandidijaze[56], međutim potrebno je više studija kako bi se utvrdo tačan uticaj pojedinačnog antioksidansa na prevenciju parodontopatije. Velika parodontalna studija sprovedena na Medicinskom i dentalnom univerzitetu u Tokiju pokazala je to da askorbinska kiselina može pojačati aktivnost i povećati ekspresiju α2β1 integrina.

Paillaud et al. discovered another evidence of increased risks of periodontitis caused by vitamin C deficiency[54]. Moreover, it has been found that mild deficiency of vitamin C is associated with extensive gingival outgrowth in the presence of metabolic syndrome and severe periodontal infection[55]. In addition to it, authors have shown an association among deficiency of vitamin C and gingivitis, ulcer in the oral cavity and several gingival abnormalities (spongy, bleeding, abnormal redness)[21,53]. Vitamin C deficiency can also be one of the most significant independent risk factors for oral candidiasis[56]. But more studies are needed to understand the impact of every exact antioxidant in periodontitis prevention. In a huge study of periodontology atTokyo Medical and Dental University, it was found thatascorbic acid may enhance alkaline phosphatase activity in periodontal ligament cells and also may increase the expression of α2β1 integrin.

To je veliki receptor za kolagen tip I, koji može da obezbedi osteoblastnu diferencijaciju ćelija parodontalnog ligemanta modulacijom interakcije kolagen tipa I-α2β1 integirin[57]. Shiga i sar., sugerišu to da askorbinska kiselina dovodi do odnovnog pojačanja u nivou kolagane tip I, ali ne može da poveća aktivnost alakalne fosfataze ili osteoklasnte m RNK u ćelijama parodontalnog ligamenta[58].

### *Vitamin A*

Vitamin A je od značaja za očuvanje epitelnih tkiva, te njegova deficijencija može dovesti do gingivitisa, gingivalne hipoplazije, proliferacije vratnog epitela i resorpcije alveolarnih delova vilice[59]. Prema Chapple i sar., ispitivanjem 11.480 odraslih osoba tokom trećeg Nacionalnog ispitivanja zdravstvenog stanja i ishrane (NIZSI III), utvrđeno je da je teška forma parodontopatije povezana sa likopenom, α-karotenom, β-karotenom, β-kriptoksantinom i deficitom vitamina A[60]. Analiza četvrtog Korejskog Nacionalnog ispitivanja zdravstvenog stanja i ishrane pokazala je to da deficit vitamina A može biti povezana sa parodontopatijom kod mladih žena[61]. Proteini, malnutricija i deficit vitamin A mogu izazvati atrofiju pljuvačnih žlezda, što redukuje protok pljuvačke i puferski kapacitet pljuvačke, sa mogućim smanjenjem uloge pljuvačke u čišćenju usne duplje i puferskog uticaja na kiseline dentalnog plaka. Slično, tome deficit vitamina A, vitamina D i protein-energetska malnutricija (PEM) mogu se dovesti u vezu sa gleđnom hipoplazijom[62]. Deficit vitamina A može usloviti i kserostomiju, smanjiti otpornost na infekcije, narušiti antiinflamatorni odgovor i narušiti rast zuba[21,43]. S druge strane, višak vitamina A dovodi do heilitisa, gingivitisa i narušava zarastanje rana[63].

### *Vitamin D*

Primarna funkcija vitamina D je povećanje intestinalne apsorpcije kalcijuma i resorpcije kalcijuma na nivou bubrega, kao i regulacija metabolizma kostiju[24]. Na sličan način vitamin D povećava mineralizaciju gleđi i dentina zuba. Vitamin D ne samo da utiče na mineralnu gustinu kostiju, već ima antiinflamatorna svojstva kao i sposobnost da stimuliše produkciju antiinflamatornih peptida[64]. Slično tome, na razvoj karijesa u prisustvu ugljenih hidrata mogu uticati mikronutrijenti kao što je vitamin $D_3$.

It is a major receptor of type I collagen, which can promote the osteoblastic differentiation of periodontal ligament cells by modulating type I collagen–α2β1 integrin interaction[57]. Shiga et al. suggest that ascorbic acid causes substantial enhancement in levels of type I collagen but is unable to increase alkaline phosphatase activity or osteocalcin messenger RNA in periodontal ligament cells[58].

### *Vitamin A*

Vitamin A is important in maintaining the epithelial tissues and a deficiency of it can cause gingivitis, gingival hypoplasia, proliferation of crevicular epithelium and resorption of alveolar parts of jaws[59]. According to Chapple et al., by examining 11.480 adults from the third National Health and Nutrition Examination Survey (NHANES III), severe periodontitis was associated with lycopene, α-carotene, β-carotene, β-cryptoxanthine and vitamin A deficiency[60]. In an analysis of the Fourth Korean National Health and Nutrition Examination Survey, a deficiency of vitamin A could be associated with periodontitis in young women[61]. Protein, energy malnutrition and vitamin A deficiency can cause atrophy of the salivary glands, which reduces the flow of saliva and buffering capacity, eventually decreasing the cleansing action of saliva and ability to buffer plaque acids. Similarly, lack of vitamin A, vitamin D and protein-energy malnutrition (PEM) can be associated with enamel hypoplasia[62]. Vitamin A deficiency can also lead to xerostomia, reduced resistance to infections, depressed anti-inflammatory response and also impaired growth of the teeth[21,43]. On the other hand, excess of vitamin A can lead to cheilitis, gingivitis and impaired healing[63].

### *Vitamin D*

The primary function of vitamin D is to increase intestinal calcium absorption and calcium reabsorption from kidneys and to regulate bone metabolism[24]. In the same way, vitamin D increases teeth dentin and enamel mineralization. Vitamin D not only affects bone mineral density but also has anti-inflammatory actions and the ability to stimulate the production of anti-microbial peptides[64]. Similarly, the development of caries in the presence of carbohydrates may be influenced by micronutrients such as vitamin $D_3$.

Postoje dokazi da se vitamin D može dovsti u vezu i sa povećanim rizikom za pojavu hronične parodontopatije[65]. Prema Van der Veldenu i sar., svakodnevno konzumiranje hrane koja sadrži dovoljno antioksidanasa, vitamina D i kalcijuma može sprčiti i lečiti parodontopatiju[66]. Antiinflamatorni efekat vitamina D može pozitivno uticati na parodontalna tkiva, smanjiti parodontopatiju i gubitak zuba[67] (jačanjem potpornih struktura zuba[21]) kao i inflamacije gingive[68]. Takođe, kalciferol poseduje imunomodulatornu aktivnost, koja može da utiče na parodontalno oboljenje, dok parodontopatija utiče na sistemski imuni odgovor[69].

***Vitamin E***

Vitamin E je antioksidans čiji nedostatak može biti povezan sa oralnim kancerom[27]. Srećom, nedostatak vitamina E je retka pojava i simptomi nedostaka ovog vitamina retko se viđaju kod zdravih osoba koja dobijaju samo malu količinu vitamina E putem hrane[70]. Deficit vitamina E, sekundarno u odnosu na abetaliproteinemiju dovodi do problema kao što je slabost mišića, loša transmisija nervnih impulsa, i degeneracija retinala koja dovodi do slepila[71]. Slično tome njegova deficijencija može dovesti do supresije antiinflamatornog sistema i depresije imunog odgovora mekih oralnih tkiva[21].

***Rizične grupe od deficijencije mikronutrijentima***

Postoji dosta mikronutrijenata koji su potrebni za normalno funkcionisanje usne duplje. Postoje određena stanja prilikom kojih određene grupe ljudi mogu biti u većem riziku od deficita specifičnih vitamina ili elemenata.

***Grupa ljudi sa određenim bolestima***

Velika deo ove grupe ljudi čine ljudi sa inflamatornim oboljenjem creva, kao što je Kronova bolest i celijakija ili osobe koje su podvrgnute hirurškim zahvatima na želucu. Ovi ljudi su uskraćeni za apsorpciju određenih nutrijenata unetih hranom i u čestom su deficitu kao što je bakar[72], cink[73,74], kalijum[75], magnezijum[76], vitamin D[77], vitamin E[64], vitamin $B_{12}$[78], vitamin $B_9$[79], vitamin C[80] i vitamin $B_1$[81].

Osobe sa oboljenjem bubrega takođe su u deficitu od pojedinih nutrijenata na primer vitamin C[82], vitamin $B_6$[83] i selen[84] imaju niže

There is an evidence that vitamin D can be related to increased risk of chronic periodontitis[65]. According to Van der Velden et al., consuming enough daily nutrition that covers sufficient antioxidants, vitamin D and calcium can prevent and treat periodontitis[66]. Anti-inflammatory effects of vitamin D may have positive effects in periodontal tissues, in decreasing periodontal disease and tooth loss[67] (by increasing strength to anchor toot structure[21]) as well as gingival inflammation[68]. Also, calciferols have an immunomodulatory activity that can affect the periodontal disease as well, while periodontitis influences the systematic immune response[69].

***Vitamin E***

Vitamin E is an antioxidant whose deficiency may be associated with oral cancer[27]. Fortunately, vitamin E deficiency is a rare situation and deficiency symptoms have not been found in healthy people who obtain even little vitamin E from their diets[70]. Vitamin E deficiency, secondary to abetalipoproteinemia causes problems like muscle weakness, poor transmission of nerve impulses, and retinal degeneration that leads to blindness[71]. Similarly, its deficiency can lead to suppressed anti-inflammatory system and depressed immune response of oral soft tissue[21].

***Risk groups for micronutrient deficiencies***

There are a lot of micronutrients that are required for the proper functioning of the oral cavity. There exist certain conditions, when a particular group of people could be at higher risk of being deficit in specific vitamins or elements.

***Groups with certain diseases***

One of the major group of people is individual with inflammatory bowel disease, like Crohn's disease and celiac disease, or an individual who has undergone through gastric surgery. These people are abstained from absorbing proper nutrients from the consumed food and frequently lack copper[72], zinc[73,74], potassium [75], magnesium[76], vitamin D[77], vitamin E[64], vitamin $B_{12}$[78], vitamin $B_9$ [79], vitamin C [80] and vitamin $B_1$[81].

People suffering from kidney failures are also in the risk of lacking some nutrients.

serumske vrednosti kod pacijenta sa terminalnim bubrežnim oboljenjem jer se određena količina selena eliminiše hemodijalizom. Vitamin C i aktivna forma vitamina $B_6$ takođe ima pojačani gubitak putem mokraće kada je funkcija bubrega narušena[82,83].

Dijabetes je sledeće oboljenje koje može usloviti deficit u pojedinih nutrijentima. Kod dijabetičara, postoji povećani klirens vitamina $B_1$[85] i magnezijuma[86]. Slično, paciijenti sa uznapredovalim karcinomima gube veliku količinu krvi, što dovodi do gubitka gvožđa[87]. Osim toga, odrasle osobe mogu imati deficit vitamina $B_1$ usled smanjene apsorpcije[88,89] odnosno vitamina D usled smanjene sposobnosti kože da ovaj vitamin sintetiše efikasno, kao što je to slučaj kod mlađih osoba[90].

***Grupa ljudi sa posebnim fiziološkim stanjima***

Veliki deo grupe ljudi sa posebnim fiziološkim stanjima čine trudnice i novorođenčad. Trudnice imaju veliku potrebu za određenim vitaminima i hranljivim sastojcima, koje, ako se ne nadoknade, lako mogu dovesti do deficita vitamina A[91], vitamina $B_9$[92], vitamina $B_{12}$[93], gvožđa[94] i cinka[95]. S druge strane, novorođenčad ima mali depo nekih vitamina i hranljivih sastojaka, a zbog njihove specifične ishrane oni su u velikom riziku od nedostatka vitamina C[96], vitamina $B_{12}$[93], vitamina E[97], vitamina A[98–100], vitamina D[101] i gvožđa[102,103].

Druga grupa pojedinaca povezana je sa široko rasprostranjenim društvenim problemom, alkoholizmom Poremećaji upotrebe alkohola obično sprečavaju prekid metabolizma cinka[104], vitamina $B_1$[105], folata [106]. Hronični alkoholizam takođe može dovesti do povraćanja, dijareje i bubrežne disfunkcije, što rezultira gubljenjem hranljivih sastojaka poput magnezijuma[107], folata[106]. Konačno, metaboliti alkohola mogu se takmičiti sa aktivnim oblicima nekih vitamina, poput vitamina $B_6$, te postaje podložan hidrolizi[108].

***Vegetarijanci i vegani***

Nemoguće je zanemariti još jednu grupu, tačnije dve grupe, koje su u riziku od nedostatka mikroelemenata - vegetarijanci i vegani[109]. Nedostatak ribe u ishrani u velikoj meri povećava rizik od n edostatka vitamina D kod vegana[110]. Vegetarijanci delimično ispunjavaju svoje potrebe za kalciferolom

For example, vitamin C[82], vitamin $B_6$[83] and selenium[84] have lower serum concentration in the patients suffering from terminal kidney disease because some amount of selenium is removed in haemodialysis. Vitamin C and the active form of vitamin $B_6$ also have a high urinary loss if renal functions are impaired[82,83].

Diabetes is the next disease, which can cause a deficiency in some nutrients. In diabetic patients, there is increased clearance of vitamin $B_1$[85] and magnesium[86]. Similarly, cancer patients with disintegrating tumour lose a high amount of blood, making them deficient in iron[87]. Furthermore, older individuals can lack vitamin $B_1$ due to its decreased absorption[88,89] and vitamin D due to the decreased ability of their skin to synthesize it as efficiently as the skin of young people[90].

***Groups with certain physiological state***

A major group of people with specific physiological states are pregnant women and infants. Pregnant women have a high demand for some vitamins and nutrients, if not replenished, they can easily have a deficiency of vitamin A[91], vitamin $B_9$[92], vitamin $B_{12}$[93], iron[94] and zinc[95]. On the other hand, infants have small storage of some vitamins and nutrients, and due to their specific diet, they are at higher risk of having deficiency of vitamin C[96], vitamin $B_{12}$[93], vitamin E[97] vitamin A[98–100], vitamin D[101] and iron[102,103].

Another group of individuals is related to a widely spread social problem, alcoholism. The alcohol use disorder usually impedes the abruption of zinc[104], vitamin $B_1$[105], folate[106]. Chronic alcoholism can also lead to vomiting, diarrhoea, and renal dysfunction, resulting in depletion of nutrients like magnesium[107] or folate[106]. Finally, metabolites of alcohol can compete with active forms of some vitamins, like vitamin $B_6$, which makes it more susceptible to hydrolysis[108].

***Vegetarians and vegans***

It is impossible to ignore one more group, more precisely - two groups that have their own risks of micronutrient deficiencies - vegetarians and vegans[109]. Lack of fish in the diet greatly increases the risk of vitamin D deficiency in vegans[110]. Vegetarians partially meet their calciferol needs with eggs[111]. Although there is a risk of deficiency of vitamin D for people living in high latitudes with any diet[112].

konzumiranjem jaja[111]. Takođe postoji rizik od nedostatka vitamina D kod ljudi koji žive na većim geografskim širinama bez obzira na ishranu[112].

Sa druge strane, nedostatak vitamina D značajno smanjuje apsorpciju kalcijuma, zbog čega vegani najverovatnije imaju manjak kalcijuma[113]. Štaviše, biljni derivati često sadrže fitinsku i oksalnu kiselinu, što sprečava apsorpciju kalcijuma, magnezijuma, cinka i drugih metala[37,114,115] Nasuprot tome, vegetarijanci imaju tendenciju da konzumiraju velike količine visokodostupnog kalcijuma[116] i malo više vitamina D od vegana [117]. Vegetarijanci i vegani takođe su podložniji i nedostataku selena[118,119].

Još jedan kritičan mikronutrijent za vegetarijance, a posebno za vegane je vitamin $B_{12}$. Ovaj vitamin se u biljkama ne akumulira u dovoljnim količinama. Stoga je jedini izvor za ljude hrana životinjskog porekla[120].

Postoje određene grupe ljudi sa određenim potrebama u ishrani, na primer dijabetičari i gojazni pacijenti zahtevaju znatno veće količine hroma i vanadijuma [121,122], a vegetarijanci i vegani imaju veću verovatnoću da imaju nedostatak ω-3 PUFAs[123] i joda[124,125], u odnosu na ljude na standardnom režimu ishrane. Međutim, nisu pronađeni značajni efekti ovih mikroelemenata na usnu duplju.

Slično tome , adekvatan unos mikroelemenata (cinka, bakara, vitamina C , vitamina A, vitamina E) ne samo da održava higijenu usne duplje , već održava i nivo antioksidansa, što smanjuje zapaljenski proces u usnoj duplji[126]. Treba napomenuti to da ostatak mikronutrijenata ne treba zanemariti, jer svi oni imaju sistemski efekat, koji takođe na kraju utiče na usnu duplju. U članku smo razmotrili samo one mikroelemente koji imaju direktne efekte na usnu duplju i čiji su efekti dobro utvrđeni kliničkim studijama.

Vitamin D deficiency, on the other hand, significantly reduces calcium absorption, that's why vegans are likely to be calcium deficient[113]. Moreover, plant derivatives often contain phytic and oxalic acids, which impedes the absorption of calcium, magnesium, zinc and other metals[37,114,115]. In contrast, vegetarians tend to consume large amounts of highly available calcium[116], and a little more of vitamin D than vegans[117]. Vegetarians and vegans are also more prone to selenium deficiency[118,119].

One more critical micronutrient for vegetarians, and especially for vegans, is vitamin $B_{12}$. The vitamin is not accumulated in plants in enough amounts. Therefore, its only source for humans is animal-derived food[120].

There are certain groups of people with specific diet requirement. For instance, diabetic and obese patients require significantly higher amounts of chromium and vanadium[121,122], and vegetarians and vegans are more likely to be deficient in ω-3 PUFAs[123] and iodine[124,125] than omnivores. However, the significant effects of these micronutrients on the oral cavity were not found.

Similarly, adequate intake of micronutrients (zinc, copper, vitamin C, vitamin A, vitamin E) not only sustain hygiene of the oral cavity but also maintain antioxidant level, which decreases inflammatory process in the oral cavity[126]. It is to be noted that the rest of the micronutrients should not be ignored, since all of them have a systemic effect, which also eventually affects the oral cavity. The article has considered only those micronutrients which have direct effects on the oral cavity and whose effects have been well-established by clinical studies.

## *Zaključak*

Zbog znatno većeg rizika od poremećaja u metabolizmu kalcijuma, usled nedostatka vitamina D i slabe apsorpcije kalcijuma u crevima, vegani bi trebalo da budu izuzetno oprezni u pogledu metabolizma minerala tvrdih zubnih tkiva. i nedostatak selena kod vegetarijanaca i vegana takođe povećava rizik od kvarenja zuba.

Deca, trudnice i dojilje takođe treba da budu svesni depresije antiinflamatornog i imunološkog odgovora mekih tkiva usne duplje, zato što su ove kategorije često u deficitu vitamina C, $B_{12}$, E, A, D i gvožđa.

Slično tome, ljudi koji konzumiraju alkohol trebalo bi da budu oprezni u pogledu statusa vitamina $B_1$, folata, cinka i magnezijuma i preduzmu odgovarajuće mere predostrožnosti, pre svega upotrebom suplemenata deficitarnih nutrijenta. Nedostatak vitamina $B_9$ i magnezijuma povećava rizik od parodontopatije, a nedostatak cinka može prouzrokovati smanjenje osećaja ukusa , ulceracije, zaravnjenje filiformnih papila i kserostomiju.

Dalje, osobe sa hroničnim inflamatornim bolestima creva treba da budu svesne da su u deficitu sa cinkom, kalijumom, magnezijumom, vitaminima D, E, $B_{12}$, $B_9$, C i vitaminom $B_1$. Nedovoljna količina vitamina C, vitamina $B_9$, vitamina E, vitamina D i magnezijuma može dovesti do parodontalne bolesti, gingivitisa, ulceracija u usnoj duplji, pa čak i do depresije antiinflamatornog i imunološkog odgovora mekih tkiva usne duplje. S druge strane, angularni heilitis uzrokuje nedostatak vitamina $B_1$ i vitamina $B_{12}$, a rizik od oralnog karcioma verovatno će biti povećan usled deficita vitamina $B_9$ i vitamina E. Dalje, kalijum je jedan od krivaca za nastanak karijesa, dok je cink krivac za zaravnanje filiformnih papila, ulceraciju i kserostomiju.

Konačno, ljudi sa oboljenjem bubrega treba da vode računa o statusu vitamina C, vitamina $B_6$ i selena u cilju sprečavanja depresije antiinflamatornog i imunološkog odgovora mekih tkiva usne duplje, parodontalne bolesti i karijesa.

Dijabetičari se često mogu suočiti sa angularnim heilitisom, koji nastaje kao posledica deficit vitamina $B_1$. Još jedan čest problem kod dijabetičara je deficita magnezijuma, koji povećava rizik od pojave parodontopatije, naročito u ovoj populaciji.

## *Conclusion*

Due to significantly higher risk of impaired calcium metabolism as a result of vitamin D deficiency, and poor absorption of calcium in the intestine, vegans should be extremely careful about mineral metabolism in hard tissues. Selenium deficiency also increases the risk of tooth decay in vegetarians and vegans.

Children, pregnant women and breastfeeding mothers should also be aware of depressed anti-inflammatory and immune response of oral soft tissues because they often lack vitamins C, $B_{12}$, E, A, D and iron.

Similarly, people who indulge in alcohol should be careful about their status of vitamin $B_1$, folate, zinc and magnesium, and take a preliminary precaution by taking their supplements. Lack of vitamin $B_9$ and magnesium increase risk of periodontitis, and zinc deficiency can cause a decrease in taste sensation, ulcers, flattened filiform papillae and xerostomia.

Furthermore, individuals with chronic inflammatory bowel diseases should be aware of developing zinc, potassium, magnesium, vitamin D, vitamin E, vitamin $B_{12}$, vitamin $B_9$, vitamin C and vitamin $B_1$ deficiency. Insufficient amount of vitamin C, vitamin $B_9$, vitamin E, vitamin D and magnesium can lead to periodontal disease, gingivitis, ulcer of the oral cavity and even depressed anti-inflammatory and immune response of oral soft tissues. On the other hand, angular cheilosis is caused by lack of vitamin $B_1$ and vitamin $B_{12}$, and oral cancer risk is likely to be increased in vitamin $B_9$ and vitamin E deficient state. Furthermore, potassium deficiency is one of the culprits for dental caries, while zinc deficiency is the culprit for flattened filiform papillae, ulcers, and xerostomia.

Finally, people with kidney diseases ought to take care of vitamin C, vitamin $B_6$ and selenium status for preventing depressed anti-inflammatory and immune response of oral soft tissues, periodontal disease and dental caries respectively.

Diabetic patients can often face with angular cheilosis due to vitamin $B_1$ deficiency. Another common problem among diabetic patients is magnesium deficiency, which increases periodontitis risks especially in this population.

***Conflict of interest***

Declarations of interest: none

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