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Dietary antioxidants for chronic periodontitis prevention and its treatment. A review on current evidences from animal and human studies

Antioxidantes dietéticos para la prevención de la periodontitis crónica y su tratamiento. Una revisión de las evidencias actuales procedentes de estudios en animales y humanos

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RESUMEN

Objetivos. Dada la relación existente entre periodontitis crónica y altos niveles de estrés oxidativo, esta revisión pretende clarificar qué papel puede desempeñar la ingesta de los diferentes antioxidantes de la dieta en el mantenimiento de un periodonto saludable y en la reducción del riesgo de padecer periodontitis crónica, así como el posible uso de terapias dietéticas basadas en estos para el tratamiento de dicha enfermedad.

Métodos. Se utilizó la base de datos de la National Library of Medicine, Washington, DC (MEDLINE: PubMed) y todos los estudios en animales y humanos tratando el tema de interés en escritos Inglés disponibles online desde la creación de la base de datos hasta Mayo de 2015 fueron recopilados.

Resultados. Los antioxidantes analizados a este respecto incluyen a la vitamina C, la vitamina A, algunos carotenoides y polifenoles, y el coenzima Q; así como los minerales, hierro, cobre y zinc que forman parte de enzimas antioxidantes. Aun así hay una escasez generalizada de estudios con pocos estudios en humanos, la mayoría de tipo observacional. Entre los diferentes antioxidantes, la vitamina E y los polifenoles parecen ser los que más evidencias a favor de su efecto beneficioso suman, pero en general los estudios son insuficientes para descartar o establecer qué antioxidantes son útiles y cuáles no.

Conclusiones. En general, los datos presentados indicarían que los antioxidantes de la dieta resultan beneficiosos para la salud periodontal, al menos bajo ciertas circunstancias. Sin embargo se necesitan más estudios para establecer la relación entre la periodontitis crónica y cada antioxidante concreto así como para diseñar intervenciones dietéticas útiles en la gestión de esta enfermedad.

Palabras clave: Gingivitis, Enfermedad periodontal, Micronutrientes, Fitoquímicos, Suplementos dietéticos

ABSTRACT

Objectives. Given the relationship between chronic periodontitis and high levels of oxidative stress, this review aims to clarify what role can played the dietary intake of different antioxidants in maintaining a healthy periodontium and in reducing chronic periodontitis risk, as well as possible use of dietary therapies based on them for this disease treatment.

Methods. The database of the National Library of Medicine, Washington, DC (MEDLINE PubMed) was used and all the studies in animals and humans are on the subject of interest in English writing online available from inception of the database until May 2015 were collected.

Results. Antioxidants analyzed in this regard include vitamin C, vitamin A, carotenoids and some polyphenols, and coenzyme Q; as well as minerals iron, copper and zinc that are constituents of antioxidant enzymes. Still, there is a paucity of studies with few human studies, mostly observational. Among the various antioxidants, vitamin E and polyphenols seem to have more evidence for its beneficial effect, but

in general the studies are insufficient to rule out or establish what antioxidants are useful and which are not.

Conclusions. Overall, the data presented indicate that dietary antioxidants are beneficial for periodontal health, at least under certain circumstances. However more studies are needed to establish the relationship between chronic periodontitis and each specific antioxidant and to design useful dietary interventions for this disease management.

Keywords: Gingivitis, Periodontal disease, Micronutrients, Phytochemicals, Dietary supplements

INTRODUCTION

Chronic periodontitis is a chronic disease associated to aging that represent the major cause of tooth loss in adults[1] and it may constitute a risk factor for other pathologies such as cardiovascular diseases[2,3]. It has been defined as an infectious disease resulting in inflammation within the supporting structures of teeth and progressive attachment and bone loss[4]. As part of this process, prior to periodontitis, the first clinical manifestation to appear is gingivitis that has been defined as an inflammation of the gingiva in which the junctional epithelium remains attached to the tooth at its original level[5]. Overall, this disease begins as an initial response to bacterial infection is a local inflammatory reaction that activates the innate immune system[6,7]. Amplification of this initial localized response results in the release of an array of cytokines and other mediators and propagation of inflammation through the gingival tissues[6,7]. The failure to encapsulate this ''inflammatory front'' within gingival tissue results in expansion of the response adjacent to alveolar bone[7]. Lastly, the inflammatory process drives the destruction of connective tissue and alveolar bone that is the cardinal sign of periodontitis[8]. Along with bone loss, this disease is characterized by pocket formation and/or gingival recession[4]. As the connective tissue attachment to the tooth breaks down, the junctional epithelium migrates in an apical direction and a periodontal pocket forms, which becomes lined by pocket epithelium with in-growth of rete pegs into the surrounding connective tissue[9].

In spite of the absence of studies quantifying reactive oxygen species (ROS) directly due to the difficulties inherent in detecting them[10], researches measuring the biomarkers generated by ROS reacting with different biomolecules have indicated a positive association between oxidative stress and periodontitis[11-14]. At the same time, less antioxidant status has been noted[15-16]. Additionally, different studies have provided evidences for several mechanisms explaining how high oxidative stress levels could contribute to periodontitis pathogenesis. On one hand, ROS at high levels, or chronically produced, can result in direct damage to cells and the extracellular matrix[17-21]. The accumulation of them could disrupt both, soft and calcified connective tissues of the peridontum (i.e. gums and alveolar bone). Degradation products found in studies analyzing gingival crevicular fluid[22–26] and tissue extracts [21,27] from periodontitis patients are in consistency with this. However, it is important to note that the presence of collagen metabolites in gingival crevicular fluid could also be the result of a combination of proteolysis by host and bacterial collagenases at least in part, though oxidative damage may make a direct or indirect contribution to their production[10]. On the other hand, products of this oxidative damage to matrix and serum protein can lead to further ROS-induced damage by their priming and chemotactic actions on neutrophils[10] and alter different fibroblasts functions[28]. According to that, it has been suggested that oxidation-dependent changes in collagen within the periodontal connective tissues could retard neutrophil migration through the tissues and increase their potential to produce ROS [10]. In addition, it has been reported that certain ROS activate osteoclasts[29] and promote osteoclast formation *in vitro*[30]. Lastly, some data also support that ROS directly can damage on tissue inhibitor of matrix metalloproteinases or induce alterations in matrix metalloproteinase expression [31–33] as occurs in other tissues[34, 35–37].

As it is well known, humans and other organisms have effective defense systems to deal with continuous ROS to which they are exposed. Specialized defense factors to deal with the high oxidant challenge present in the different organisms are referred to as antioxidants. Altogether, antioxidant system is complex and there are different types of antioxidants with different mechanism. Some antioxidants prevent the generation of ROS, some are enzymes that destroy ROS, some are small water-soluble molecules that act as reducing agents to «neutralize» free radicals, and some absorb electrons or excess energy from ROS and «dissipate» this within their complex lipophilic structure[38,39]. However, although our intrinsic antioxidant defense is highly effective, dietary input of antioxidants is needed[40] and some antioxidant present in food are essentials nutrients. Still, conceptually at least, the other antioxidants that evolved to deal with oxidant challenge in plants could have a role to play in defending human tissues from this same challenge, augmenting our endogenous antioxidant system in the prevention of oxidative stress[40]. Actually, protection by various antioxidants (or, better, diets containing antioxidants) against different chronic diseases and cancer has been attributed to their antioxidant capacity[41]. Low intakes of one or more of these antioxidant nutrients could reduce the body's defenses against free radical damage and

increase susceptibility to health problems associated with free radical damage [42]. This concept that enhanced optimal antioxidant defense of the body lowers risk of disease and slows biological aging[40] would be apply to chronic periodontitis. For this reason, the present review is aimed to clarify what role is played by different antioxidant dietary intake in promoting periodontal health and/or reducing the chronic periodontitis risk, as well as the possible use of dietary interventions based on for this disease treatment.

MATERIALS AND METHODS

For this review, a search was conducted in the electronic database of National Library of Medicine, Washington, DC (MEDLINE: PubMed) aimed to find both published studies in English language from inception of the database until May 2015. All relevant human and animal studies *online* available on the association of periodontitis or gingivitis and dietary antioxidant intake were included. For this, the following theme was introduced: (periodontitis OR gingivitis) AND antioxidant AND (diet OR nutrition OR intake). However when they clearly assessed other forms periodontal disease, as aggressive periodontitis, were excluded.

RESULTS

Ascorbic acid

L-ascorbic acid is also called vitamin C since is an essential nutrient for humans and other animals. As ascorbate, it is an enzymatic cofactor in a range of essential metabolic reactions in all animals and plants [43,44], but this vitamin is also known to act as antioxidant in living organisms [44]. There are several reason making vitamin C an effective antioxidant: the low reduction potentials of ascorbate and ascorbyl radical (formed by one electron oxidation of ascorbate), the low reactivity of ascorbyl radical that readily dismutates to ascorbate due to resonance stabilization of the unpaired electron, and the existence of multyple pathways to regenerate ascorbate from both the ascorbyl radical and dehydroascorbic acid. These last include enzyme-dependent systems as the NADH-dependent semidehydroascorbate reductase and the NADPH-dependent selenoenzyme thioredoxin reductase; as well as enzyme-independent pathways including reduced gluthatione (GSH) and lipoic acid, thioredoxin reductase and the GSH-dependent enzyme glutaredoxin. On the other hand, ascorbic acid also behaves as a pro-oxidant since it has been shown to reduce transition metals such as cupric ions to cuprous and ferric ions to ferrous during conversion from ascorbate to dehydroxyascorbate *in vitro*. This reaction can generate superoxide and other reactive oxygen species. However, in the body, free transition elements are unlikely to be present while iron and copper are bound to diverse proteins [45].

Research into the relationship between vitamin C and periodontal alterations comes from as far as the eighteenth century when it was observed that scurvy was fully recovered after a treatment with oranges and lemons [46] which are directly related to its role in collagen synthesis [44.] More recently, different observational studies evaluating effects of dietary levels of this nutrient on a variety of outcomes related to periodontitis have been performed in humans, but findings reported by them have been different. Some observational studies have not found clear associations with periodontitis severity [47–49] or gingivitis presence [48,49]. However, all are cross-sectional and in some cases intake estimates were obtained from a single 24-hour dietary recall [47]. In contrast, other have displayed a negative association between vitamin C intake and periodontitis supporting a positive role of vitamin C on periodontal health [50,51]. Among them, there a cohort study indicating an inverse relationship between vitamin C intake and incidence rate ratio of disease progression from Niigata city (Japan), but it was performed in 75 years old persons [51]. Supporting this finding, there is other cross-sectional study reported an inverse dose-dependent relationship between vitamin C intake and risk of periodontitis in a sample of 12,419 subjects from NHANES III [50], a representative survey of the U.S. non-institutionalized population of adults aged 20-90 years old. This relationship, although statistically significant, was modest when the entire population was assessed. However, when smokers and non-smokers were evaluated, a slightly greater increased risk for periodontal disease was seen only in current and former tobacco users [50].

Regarding experimental studies, animal research conducted in rats (*Rattus norvergicus*) fed on vitamin C-supplemented or -deficient diets by incorporated it to drinking water have shown positive effects for this nutrient [52,53]. In one, periodontitis was experimentally induced by ligatures placement around molars for 4 weeks and dietary treatment (1g/l vitamin C) started after removing ligatures. After 6 weeks, it was noted an improvement of reduced to oxidized glutathione ratio (GSH/GSSG) and a decrease in 8-hydroxy-2′ -deoxyguanosnie (8-OHdG) levels in gingival tissue as well as plasma reactive oxygen metabolites levels which correlated to an increase in plasma vitamin C level indicating a oxidative stress decrease at both, systemic and local levels. Notwithstanding, the degrees of apical migration of the junctional epithelium and alveolar bone resorption remained unaffected by supplements, although the densities of polymorphonuclear leukocytes and active

(TRAP-positive) osteoclasts showed a 76 and 74% decrease, respectively [52]. In contrast, similar vitamin C dosages have shown to prevented the effect of high-cholesterol diet for 12 weeks on alveolar bone density and osteoclast differentiation which correlated with decreased serum 8-OHdG expression 53. In spite of this last result in animals, none intervention study in humans has reported clear positive effects for this nutrient. In 1965, a trial in children showed chewing on vitamin C-enriched tablets not improve effect on Russell's peridontal index, an index of periodontitis severity, compared to mannitol-containing tablets that were used as placebo[54]. More recently, a cross-over trial have shown that chewing sugar free gum contained vitamin C for 3 months after scaling treatment to remove all supragingival and subgingival calculus reduces gingival bleeding but measures of pocket depth or attachment level were not taken, so treatment implications were not deeply known[55.] On the other hand, no effects also have been noted in other two investigations in patients that received root and planning therapy before a period of vitamin C supplementation [56,57].

Carotenoids and vitamin A

Carotenoids are a group of nearly 600 compounds lipid-soluble plant pigments found naturally in many foods[58]. There are carotenoids either oxygenated or non-oxygenated hydrocarbons containing at least 40 carbons and an extensive conjugated double bond system and they can be found esterified to fatty acids or unesterified in plant tissues[59]. The predominant non-polar functional carotenoid are alpha-carotene, beta-carotene, and lycopene are s and lutein is the primary polar functional carotenoid. From all carotenoids about 50 have provitamin A activity being beta-carotene the most important precursor. Antioxidant activity has been reported for vitamin A1 (retinol) and A2 (dehydroretinol) as well as for many pro-vitamin A compounds, including β- and α-carotenes. Moreover other carotenoids with little or no vitamin A activity, but that are found in substantial quantities in the human diet and in tissues, are also reported to have antioxidant activity including lycopene, lutein, canthaxanthin, neoxanthin, violaxanthin, astaxanthin and zeaxanthin [60]. The antioxidant activities of carotenoids and vitamin A are conferred by the hydrophobic chain of polyene units that can quench singlet oxygen, neutralize thiyol radicals, and combine with and stabilize peroxyl radicals. In general, the longer the polyene chain, the greater the peroxyl radical stabilizing ability [61]. Studies evaluating the role of this group of compounds on peridontitis from a dietary standpoint have been only observational, and results did not confirm its possible beneficial role. Furthermore, most of them only estimate vitamin A intake [47–49]. In 1976, a cross-sectional study in 56 patients from a dental clinic found a negative correlation between dietary vitamin A intake and Rusell's periodontal index [47]. Likewise, in the retrospective cohort study for two years in elderly Japanese mentioned above, it was noted a negative association between dietary beta-carotene intake and nº of teeth with periodontal disease progression, even after adjustment for several co-founders, although α-carotene intake did not show association[62]. Lastly, a survey that comparing female adolescents with and without gingivitis that assessed dietary vitamin A levels in the diet too, but no differences were observed [49]. Although there no measures to evaluate oxidative stress levels in these research, the fact of beta-carotene is the an efficient quencher of singlet oxygen [63] but vitamin A cannot quench singlet oxygen and has a very small capacity to scavenge free radicals [64,65] this fact would be consistent with the possibility that this effect is due to its antioxidant activity. However, the paucity of studies does not allow to obtain conclusions. Future efforts should be made to include some carotenoids in dietary assessments in this study type, specially in the case of and beta-carotene and lycopene that also has show an important antioxidant activity [66].

Tocopherols and tocotrienols

Tocopherols and tocotrienols are lipid-soluble food components termed as «vitamin E» as a whole. This structure is featured by a phenolic-chromanol ring linked to an isoprenoid side chain that is either saturated (tocopherols) or unsaturated (tocotrienols). In addition, it possible to distinct four primary forms of tocopherols and tocotrienols, alpha, beta, gamma, and delta that differ in the number and position of methyl groups on the phenolic-chromanol ring rendering eight isomers of vitamin E [67,68]. Vitamin E is a well-known antioxidant [69] that stops the production of ROS formed when fat undergoes oxidation [70]. The antioxidant effects of vitamin E result from the incorporation of vitamin E into cellular membranes, where it inhibits peroxidation of lipids [71,72]. There are data indicating dietary vitamin E beneficial role on periodontitis, although they only comes from cohort studies based on an elderly subset of Niigata city population [51,62]. Meanwhile, research in rats using ligature-induced periodontitis models have indicated that vitamin E supplementation for 9 days reduce oxidative stress on gingivomucosal tissue, but this no implied necessary a decrease alveolar bone loss[73]. Still, there are other studies in rice rats (*Oryzomus palustris*) that naturally present periodontitis[74] where vitamin E supplements had a protective effect on bone loss in all cases[75]. Furthermore, a recent dietary intervention in humans following mechanical treatment for chronic periodontitis have shown that adjunctive vitamin E supplementation improves periodontal healing as well as antioxidant defense represented by SOD activity both, in serum and saliva[76]. Therefore, the use of nutritional therapies based on vitamin E intake at least in combina-

tion with other periodontal therapies seems promising but many researches on this topic is needed.

Iron, copper and Zinc

Several minerals have been taken account since they have been considered as antioxidants although really they are not, but they are essential for antioxidant enzyme activity[77]. Iron is a constituent of catalase, a hemeprotein, which catalyzes the decomposition of hydrogen peroxide. Copper form part of ceruloplasmin that fights against extracellular free radicals. Further, along with zinc, it forms part of superoxide dismutase (SOD)1 that is present in cell cytosol participating in intracellular oxidative stress decrease. Likewise, zinc and manganese are the cofactors of the mitochondrial enzyme, SOD2. Lastly, this group also includes selenium with is required for gluthatione peroxidase activity [42]. Dietary intakes of iron, copper and zinc role on periodontitis were assessed in the study performed on humans by Freeland *et al*.[47], but associations with Russell's periodontal index were not found. Despite these data, association presented in this paper can be influenced by several reasons since not fasting instruction was given to patients before blood samples collection. In addition to that, dietary data may be not representative because of a dietary recall of only 24 hours. Since them, new research on this topic have been performed only for zinc in both, humans[78] and animals[79]. Regarding first, a zinc-supplemented syrup was tested that seemed to exert some beneficial effects in a double-blind randomized study in children. In spite of periodontal index scores were similar at baseline, there were more children whose scores decreased in comparison to those where they increased, whereas those receiving placebo syrup showed similar proportions. In turn, gingival index decrease was occurred in more children in the two groups [78]. In addition to this trial, research in rats also support the dietary zinc beneficial role in certain degree since zinc-deficient diets have been related to lower plaque and gingival indices scores, although probing depth remained unaffected [79]. However, the effect of dietary content of the other two minerals on chronic periodontitis it has just been object of interest as well as the use of nutritional therapy with them. Therefore, there is insufficient evidence to avoid these three nutrients and other «antioxidant» minerals in future research.

Polyphenols

Polyphenols are numerous and widely distributed molecules present in plants that contain one or more benzene rings and varying number of hydroxyl, carbonyl, and carboxylic acid groups. They commonly exist in conjugated forms with one or more attached sugar residues. The most common class of polyphenols is the flavonoids. Other types of polyphenols include catechins, thearubingens, theaflavins, isoflavones, and over 8000 others [67]. The additon of several specific polyphenols to the diet have been tested in rodents models of periodontitis. In rat models of ligature-induced periodontitis oral administration of resveratrol (*trans*-3,4′,-5-trihydroxystilbene)[80,81], mangiferin (C2-b-d-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone)[82], baicalin (7-glucuronic acid, 5,6-dihydroxy-flavone)[83], verbascoside (4,5-hydroxyphenylethanol bound to a b-(d)-glucopyranoside) and quercetin (3,5,7,3′,4′-pentahydroxyflavone)[84] have shown to reduce alveolar bone loss, which in most of cases it was accompanied by of inflammation sings[85,86]. Similar effect on alveolar bone has been observed in a mouse periodontitis model induced by *A. actinomycetemcomitans* infection for the compound[84]. Additionally, when it was measured, it was noted that this effect on bone loss correlates with reduced oxidative stress[87] or levels of enzymes that promote it like iNOS[83,87]. In particular, quercetin has shown a clear antioxidant effect in the oral cavity against NO resulting from nitrite reduction by certain oral bacteria which could extend to other compound of this type[88]. In rabbits, it has been reported a certain anti-inflammatory effect of supplementation with hydroxytyrosol. Specifically, it was reported that it reduced endothelial activation in rabbits that had developed atherosclerosis induced by a diet rich in saturated fats, but it did not improve endothelial activation and lower cellularity in gingival mucosa, which are also associated with this pathology[89]. However data about its effect on alveolar bone or periodontal oxidative stress levels was not be available. Hydroxytyrosol (3,4-dihydroxyphenylethanol) is originated during the maturation of olives, storage of the oil and preparation of table olives by hydrolysis of oleuropein[90]. In contrast with diet based on other fat sources (sunflower and fish oil), a virgin olive oil-based diet have shown to decrease alveolar bone breakdown associated with aging in rats that also displayed lower gingival lipid peroxidation [91]. At present, it is well established that the health benefits of olive oil are not concentrated solely in its fatty acid content [92], so this effect could be attributed to its hydroxytyrosol content.

Coenzyme Q

Coenzyme Q (CoQ) is a naturally occurring coenzyme formed from the conjugation of a benzoquinone ring with a hydrophobic isoprenoid chain of varying chain length, depending on the species[93]. It is found in every plant and animal cell and is located in the inner membrane system of the mitochondria, other membranes and in plasma lipoproteins[94]. Due to its ubiquitous presence in nature and its quinone structure, CoQ is also known as ubiquinone[95]. It exists in two molecular forms, ubiquinone, the oxidized form,

and ubiquinol, the reduced form, which are the basis for its antioxidant properties[96]. The well-recognized function of CoQ is mitochondrial energy coupling to produce ATP[94]. The other important function is that it acts as a primary scavenger of free radicals as it is well located in the membranes in close proximity to the unsaturated lipid chains. Less well-established functions also include oxidation/reduction control of signal origin and transmission in cells, which induce gene expression, control of membrane channels, membrane stabilization and lipid solubility[94]. Clinical trials where CoQ was orally administrated to periodontitis patients have shown to increase the CoQ concentration in gums and suppresses gingival inflammation [97,98]. The beneficial role of dietary CoQ on this diseases is supported by a more recent research in rats maintained in different dietary treatments for 2 years[91,99]. In this, addition of low-dosages of CoQ to diet decreased alveolar bone loss associated with the consumption of a n-6 fatty acid-rich diet[99]. However, the only oxidative damage marker used, reactive substances (TBARS) levels, did not show significant differences, so it is not possible to clarify that this finding was due to a decrease in oxidative stress levels. Moreover, in this animal model gums usually showed no clear sings of inflammation[91], so it is not possible to confirm its effect on gingival inflammation.

DISCUSSION

The proposal of this review was to clarify the role of the different antioxidant intake in promoting healthy aging of periodontium and/or reducing risk of chronic periodontitis as well as the use of dietary treatment based on them in its treatment. After search and read carefully information available on this topic, it has been noted a generalized paucity of studies, particularly in humans. Other added problem is that some of them not evaluate dietary intake effects on oxidative damage or antioxidant status and some antioxidants are essential nutrients that participate as coenzyme in other relevant process. Thus, in many cases, it is not possible to confirm that positive effects on periodontal tissues observed were due to their antioxidant activity.

Among different dietary antioxidant, the most studied have been vitamin C followed by vitamin A and vitamin E. Concerning vitamin C, the number of observational and animal studies suggesting clear positive effects on periodontitis[50,51,53] and reported an absence of statistical association or effect [47–49] have been similar. One reason explaining these differences could be that vitamin C intake only is relevant when subjects present some condition associated to high oxidative stress as smoking[50] or even aging[51]. Likewise, vitamin A intake role on periodontal health remain unclear. On the other hand, results from studies focused on vitamin E effect have been mostly positive [51,62,74,76]. Similarly, beneficial effect has been also reported for different polyphenols [80–84,87], as well as CoQ [99] but they only have been tested in animals, although for many their *in vivo* antioxidant effects seems due to iNOS expression or activity modulation and not to free radical scavenging. Unfortunately, at the moment, experimental interventions in humans have been reduced to vitamin C[54–57] but also for E [76] or Zinc[78], where vitamin E have result the most interesting although it were used after mechanical treatment.

CONCLUSIONS

In general, there are a paucity of studies on possible relationship between dietary antioxidants and periodontitis, particularly in humans, and they are very different. In addition many of them are observational studies that do not deepen on possible mechanisms under associations reported. Still, data presented here, altogether, would indicate that dietary intake of antioxidant is beneficial for periodontal health, at least under some circumstances. However, more studies are needed in order to establish the relationship between chronic periodontitis and each antioxidant as well as to design useful dietary interventions to manage this disease.

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