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Effects of specific nutrients on periodontal disease onset, progression and treatment

Review Paper

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Abstract

Objectives: The aim of this paper is to review the available literature pertaining to the effects of specific nutritional elements (e.g. vitamin B-complex, vitamin C and dietary calcium) on general wound healing, periodontal disease status and response to periodontal therapy.

Methods: Critical appraisal of various studies that have evaluated the effects of calcium, ascorbic acid and vitamin B-complex in wound healing and periodontal treatment.

Results: Periodontal disease onset, progression and response to therapeutic interventions have been shown to be influenced by several systemic, local and environmental modifying factors. Nutritional supplementation has been suggested as a possible influencing factor on periodontal status and wound healing. Several studies have reported various degrees of association between nutritional elements/supplements and periodontal status, and others have reported possible positive influences of nutritional supplementation on periodontal therapeutic outcomes. Future research needs to more fully explore the presence and strength of association between nutrition and periodontal health.

Conclusions: Data collected from the literature suggests that nutrient supplementation causes minimal or no side effects. However, the efficacy of prophylactic nutrient supplementation for the prevention of the onset and progression of periodontal disease, or for the enhancement of periodontal wound healing, remains to be determined.

Key words: periodontal therapy; periodontal disease; treatment; nutrition; vitamin; calcium

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Periodontal research has provided sufficient evidence indicating that chronic periodontal disease is treatable (AAP 1998). Although complete restoration of the lost periodontal tissues is the ideal endpoint of periodontal therapy, regeneration appears to be limited to specific situations and the prognosis is still largely uncertain. Therefore, the majority of periodontal treatment modalities attempt to arrest the progression of periodontal destruction in order to avoid tooth loss, and studies have shown that the great majority of treated periodontal patients have their odds of tooth loss significantly reduced (Becker et al. 1979). There are some situations, however, when periodontal therapy is not effective in arresting disease progression, and attachment and/or tooth loss occurred despite the provision of proper treatment. Periodontal research efforts have consequently attempted to identify background factors that may explain the poor response to therapy demonstrated in some patients. Several systemic, local, and environmental risk factors have been demonstrated to influence the wound healing response following periodontal therapy. Local risk factors include preexisting disease as evidenced by deep probing depths and plaque retentive areas associated with defective restorations (Grossi et al. 1994, 1995). Systemic risk factors identified by large epidemiological studies include diabetes mellitus and cigarette smoking (Genco 1996). Most of these local and systemic factors can generally be modified or modulated in order to improve the healing response following periodontal therapy (Caton 1993). However, other possibly modifiable systemic factors such as a balanced nutrition or a supplementation of nutrients have not been thoroughly evaluated in periodontal research, although reports of the possible effects of nutrient deficiency and supplementation have appeared early in the periodontal literature (Glickman 1948a, b, Waerhaug 1958). By analyzing the systemic effects of certain nutrients, it can be hypothesized that periodontal treatment could be enhanced with the addition of these nutrients to periodontal therapy, providing a safe method to potentiate the

clinical response following treatment. Therefore, the aim of this paper is to review the available literature addressing the relationship between nutrition and periodontal disease onset, progression, and response to treatment.

Role of Nutrition

Data collected by the United States Department of Agriculture from over 11,000 Americans showed that on any given day, 41% did not eat any fruit, 82% did not eat cruciferous vegetables, 72% did not eat vitamin C-rich fruits or vegetables, 80% did not eat vitamin A-rich fruits or vegetables, and 84% did not eat high-fiber grain food, like bread or cereal (Patterson & Block 1988). Food is mainly chosen based upon taste, cost, convenience, and psychological gratification, largely ignoring the needs of providing nutrients to the body. While many Americans are overfed, the majority is also poorly nourished (Quillin 1989). Based on these facts that may be more pronounced in other regions of the world, we can assume that malnutrition, or at least poor dietary habits, can be highly prevalent among periodontal patients. The effects of malnutrition on wound healing are particularly important to address, since identification of plausible influencing factors on the healing response following periodontal therapy may ultimately lead to improved patient care and treatment outcomes.

Nutritional elements implicated in the wound healing process

Specific nutritional elements that have been most strongly associated with the physiological processes of wound healing from the medical and periodontal literature include the vitamin B-complex of vitamins, vitamin C, and calcium (Table 1). An overview of the physiological properties of these nutritional elements and their possible influences on the wound healing process are presented next.

Vitamin B-complex

The vitamin B-complex refers to all of the known essential water-soluble vitamins except for vitamin C. These include thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin, folic acid and the cobalamins (vitamin B_{12}). "Vitamin B" was once thought to be a single nutrient that existed in extracts of rice, liver, or yeast. Researchers later discovered that these extracts contained several vitamins, which were given distinguishing numbers. Despite the erroneous belief that these vitamins have a special relationship to each other, each member of the B-complex has a unique structure and performs unique functions in the human body. Vitamins B_1, B_2, B_3, and biotin participate in different aspects of energy production, vitamin B_6 is essential for amino acid metabolism, and vitamin B_{12} and folic acid facilitate steps required for cellular division (Pollack 1979). Each of these vitamins has many additional functions; however, no functions require all B-complex vitamins simultaneously. Deficiencies of vitamin B-complex can cause the absence of disturbed protein, carbohydrate, and fat metabolism. Deficiencies can also decrease resistance to infection secondary to antibody formation, and some WBC functions may be impaired (Yates et al. 1998).

Table 1. Physiological effects of specific nutrients

Physiological effects	Nutrient
promoting proper carbohydrate metabolism	vit. B_1, B_3, B_5, B_7
necessary for proper function of nervous system	vit. B_1, B_2, B_3, B_5
necessary for proper function of muscular tissues	vit. B_1, B_{12}, calcium
aids in energy utilization from food	vit. B_2
helps in red blood cell formation	vit. B_2, B_6, B_{12}, folic acid
involved in fat, carbohydrate, and protein metabolism	vit. B_3, B_5, B_6
necessary for hormonal synthesis and function	vit. B_5, B_6
necessary for proper immune system function and wound repair	vit. B_6, vit. C
assists in utilization of other B-complex vitamins	vit. B_7
necessary for nucleic acid formation	vit. B_{12}, B_c
necessary for amino acid metabolism	vit. B_6, B_c
important in collagen formation and maturation	vit. C
necessary for mineralized tissues formation	calcium
aids in clotting of blood	calcium

Vitamin B_1 (thiamin): A deficiency in thiamin intake leads to a severely reduced capacity of cells to generate energy. The earliest symptoms of thiamin deficiency include constipation, appetite suppression, nausea as well as mental depression, peripheral neuropathy, and fatigue. Chronic thiamin deficiency leads to more severe neurological symptoms and to cardiovascular and musculature defects (Winston et al. 2000). Severe thiamin deficiency diseases include beriberi, which results from a diet that is carbohydrate rich and thiamin deficient, and Wernicke–Korsakoff syndrome, most commonly found in patients with chronic alcoholism due to their poor dietetic lifestyles (Bohmer 2001).

Vitamin B_2 (riboflavin): Riboflavin deficiencies are rare in developed countries due to the presence of adequate amounts of the vitamin in eggs, milk, meat, and cereals (Subar et al. 1995). Riboflavin deficiency is also often seen in chronic alcoholics due to their poor dietetic habits. Symptoms associated with riboflavin deficiency include glossitis, seborrhea, angular stomatitis, cheilosis, and photophobia.

Vitamin B_3 (niacin): A diet deficient in niacin leads to glossitis, dermatitis, weight loss, diarrhea, depression, and dementia. The severe symptoms of depression, dermatitis, and diarrhea are associated with the condition known as pellagra. Several physiological conditions (e.g. Hartnup disease and malignant carcinoid syndrome) as well as certain drug therapies (e.g. isoniazid) can lead to niacin deficiency (Carpenter 1983).

Vitamin B_5 (pantothenic acid): Deficiency of pantothenic acid is rare due to its widespread distribution in whole-grain cereals, legumes, and meat. Symptoms of pantothenic acid deficiency are difficult to assess since they are subtle and resemble those of other vitamin B deficiencies (Schwabedal et al. 1985).

Vitamin B_6 (pyridoxine): The requirement for vitamin B_6 in the diet is proportional to the level of protein consumption ranging from 1.4–2.0 mg/day for a normal adult. During pregnancy and lactation, the requirement for vitamin B_6 increases approximately 0.6 mg/day. Deficiencies of vitamin B_6 are rare and are usually related to an overall deficiency of all the B-complex vitamins (Doke et al. 1998, Moriwaki et al. 2000).

Vitamin B_7 (biotin): Biotin is found in numerous foods and is also synthesized by intestinal bacteria, making deficiencies of the vitamin rare. Deficiencies are generally seen only after long antibiotic therapies, which deplete the intestinal flora (Abraham & Kurup 1993, Velazquez et al. 1989).

Vitamin B_{12} (cobalamin): Vitamin B_{12} is synthesized exclusively by microorganisms and is found in the liver of animals bound to protein as methycobalamin or 5′-deoxyadenosylcobalamin. The vitamin must be hydrolyzed from protein in order to be active. Pernicious anemia is a megaloblastic anemia resulting from vitamin B_{12} deficiency that develops as a result of a lack of intrinsic factor in the stomach leading to malabsorption of the vitamin. The anemia results from impaired DNA synthesis due to a block in purine and thymidine biosynthesis (Andres et al. 2001, Antony 2001, Peracchi et al. 2001).

Vitamin B_c (folic acid): Deficiency results in complications nearly identical to those described for vitamin B_{12} deficiency. The most pronounced effect of folate deficiency on cellular processes is on DNA synthesis. This is due to impairment in dTMP synthesis, which leads to cell cycle arrest in the S-phase of rapidly proliferating cells, in particular hematopoietic cells, resulting in megaloblastic anemia. The predominant causes of folate deficiency are impaired absorption or metabolism or an increased demand for the vitamin. Poor dietary habits can lead to folate deficiency. Certain drugs such as anticonvulsants and oral contraceptives can impair the absorption of folate, while anticonvulsants increase the rate of folate metabolism (Marcus & Freedman 1985, Swain & St Clair 1997).

Vitamin C (ascorbic acid)

Vitamin C or ascorbic acid is essential for the formation of collagen and intercellular material, bone and teeth, and for the healing of wounds. It helps maintain elasticity of the skin, aids the absorption of iron, and improves resistance to infection (Mazzotta 1994). Humans are among the few mammals unable to synthesize ascorbic acid in the liver. Deficiency of vitamin C is called scurvy. The chief feature of the disease is that the limbs become painful and tender from the hemorrhages beneath the periosteum. Purple swellings and gingival bleeding may occur because vitamin C deficiency makes the capillaries fragile and susceptible to rupture (Thomas 1997). Scurvy is diagnosed by its symptoms, including ecchymosis of the skin, loose attachment of the periosteum, subperiosteal hemathomas, bleeding into the joint spaces, gingivitis, hemorrhages, opportunistic bacterial infections, and impaired wound healing (Vaxman et al. 1990). Vitamin C supplementation is able to reverse the symptoms of scurvy (Touyz 1984).

Dietary calcium

Calcium is the most abundant mineral in the human body. Of the body's total calcium, about 99% is in the bones and teeth, where it plays a structural role, while the remaining 1% is present in body tissues and fluids, where it is essential for cell metabolism, muscle contraction, and nerve impulse transmission. A continuous exchange of calcium exists between the skeleton, blood, and other parts of the body, and is closely controlled by specific hormones. Metabolites of vitamin D are important in this process by increasing the reabsorption of calcium by bones (Weimann & Hermann, 1999). Calcium can also bind to a wide range of proteins, altering their biological activity that makes it important in nerve impulse transmission and muscle contraction, and is also involved in blood clotting due to its activation of clotting factors. Vitamin D is needed for the absorption of dietary calcium (Doyle et al. 1996). In adults, calcium deficiency may lead to osteomalacia and osteoporosis. Osteoporosis involves loss of calcium from the bones and reduced bone density, which causes bones to be brittle and liable to fracture. A low level of calcium in the blood and tissues can cause hypocalcemia (Scheiber et al. 2001). Excess calcium in the blood can cause nausea, vomiting, and calcium deposition in the heart and kidneys, as a result of excessive doses of vitamin D (Yates et al. 1998).

Table 2. Effects of nutrition on wound healing processes

Author	Sample	Comparision	Results
Weimann & Hermann (1999)	cultured fibroblasts	vit. B_5 (+) versus normal culture medium	the migration of cells into a wounded area was dose-dependently stimulated by vit. B_5
Lacroix et al. (1988)	cultured fibroblasts	vit. B_5 versus vit. C versus both added to culture medium	vit. B_5 increased proline precipitation. synergistic effect between vit. B_5 and vit. C
de Lucia et al. (1988)	rats	vit. B_6 (+) versus normal diet	earlier formation and maturation of granulation tissue and bone in vit. B_6 (+) animals
Graf et al. (1992)	rats	vit B_c (+) versus normal diet	improved wound healing after vit. B_c (+)
Alvarez & Gilbreath (1982a, b)	rats	vit. B_1 (−) versus normal diet versus vit. B_1 (+)	faster wound maturation for vit. B_1 (+) rats
Aprahamian et al. (1985)	rabbits	vit. B_5 (−) versus normal diet versus vit. B_5 (+)	increased aponeurosis strength and greater fibroblast proliferation for vit. B_5 (+) rabbits
Vaxman et al. (1990)	humans	vit. B_5 (+) versus normal diet versus vit. C (+)	higher breaking energy of scars in Vit. B_5 group due to more stable and solid collagen formation
Collins et al. (1989)	rats	vit. B_3 (+) versus saline solution	vitamin B_3 may increase random flap survival and may also influence repositioned flaps

(+) = supplementation; (−) = deficiency.

Effects of nutritional supplements on wound healing

Several studies in the medical literature have examined the physiologic effects of specific nutritional supplements on the healing of surgical wounds (Table 2). Alvarez & Gilbreath (1982a, b) conducted biochemical and mechanical experiments to determine the effect of dietary thiamine on collagen maturation during wound repair in rats. Rats were divided into three dietary groups and fed either a thiamine-deficient diet ($-B_1$), a thiamine-deficient diet supplemented with 1 mg thiamine-HCl (+B1), or a thiamine-deficient diet supplemented with 3 mg thiamine-HCl (+3B1). When −B1 rats were demonstrated to be deficient in urinary thiamine, all animals were wounded. Ten days after wounding the animals were sacrificed and the tissues harvested. Significant differences were observed in lysyl oxidase activity between −B1 and +B1 in both wounded and unwounded tissue, and in isometric shrink tension between −B1, +B1, and breaking strength between all three dietary treatment groups. The changes observed in this study demonstrated a definite involvement of thiamine in wound repair and scar development (Alvarez & Gilbreath, 1982a, b).

Aprahamian et al. (1985) investigated the effect of vitamin B_5 supplementation and deficiency on wound healing in rabbits. Chronic pre- and postoperative vitamin B_5 supplementation significantly increased aponeurosis strength after surgery. Furthermore, the fibroblast content of the scar became significantly greater during the fibroblast proliferation phase after vitamin B_5 supplementation. These data suggest that vitamin B_5 induces an accelerating effect of the normal healing process. The mechanism responsible for this improvement seems to be an increase in cellular multiplication during the first postoperative period (Aprahamian et al. 1985).

Lacroix et al. (1988) analyzed the role of vitamin B_5 and vitamin C on wound healing processes, and the effects of these vitamins upon the growth of fibroblasts obtained from human fetal skin or foreskin. The rate of cell growth remained identical when vitamin B_5 or vitamin C was added to the culture medium. Vitamin B_5 increased the basal incorporation of 14C proline into precipitated material, while vitamin C did not modify this action. However, when cultures were incubated with vitamin B_5 and vitamin C, the release of intracellular protein into the culture medium increased. These results suggest that the combined use of these two vitamins might be of interest in postsurgical therapy and in wound healing (Lacroix et al. 1988).

de Lucia & Martinelli (1988) studied the effects of vitamin B_6 supplementation in rats. Histological analysis of experimental group sections when compared with the controls showed that the blood clot and fibrin net were substituted more rapidly by the granulation tissue in vitamin B_6-supplemented animals (de Lucia & Martinelli 1988). Collins et al. (1989) observed the effects of vitamin B_3 supplementation in an abdominal pedicle skin flap model. Sprague–Dawley rats were divided into five groups. Animals received either 0.6 cm^3 cc of saline or doses of nicotinamide for 16 days (14 days preoperatively and 2 days postoperatively): 25, 50, 100, or 200 mg b.i.d. The results demonstrated that vitamin B_3 may increase random flap survival and may also influence repositioned flaps (Collins et al. 1989).

Graf et al. (1992) subjected male Wistar rats to colonic resection and supplementation of vitamin B_c. Treatment was started immediately after surgery and continued until the animals were sacrificed at 3 or 7 days. Breaking strength in animals receiving vitamin B_c was similar to that in the control group. In this model colonic healing was impaired after intraperitoneal 5-fluorouracil administration, but when folic acid was added, no further deterioration occurred (Graf et al. 1992).

Vaxman et al. (1990) studied the effects of high doses of vitamin C (1 or 3 g/day (group 1)) and vitamin B_5 (0.2 or 0.9 g/day (group 2)) on the wound healing process of human skin. More than 80 mechanical, biological, and histological parameters were investigated in both preoperated skin and scars. The results showed that the breaking energy of scars was higher in the vitamin B_5 group, and that breaking energy and vitamin treatment were directly correlated (Vaxman et al. 1990, 1995, 1996). From these studies, it was suggested that vitamin B_5 supplementation creates more solid and resistant scars, presumably by producing a more stable collagen structure. Weimann & Hermann (1999) also investigated the effect of vitamin B_5 on the migration, proliferation, and protein synthesis of human dermal fibroblasts. The migration of cells into a wounded area was dose-dependently stimulated by vitamin B_5. In addition, cell division was increased, and protein synthesis was changed (Weimann & Hermann, 1999). These results suggest that higher quantities of vitamin B_5 are locally required to enhance wound healing.

These studies have implicated that certain vitamin supplements (mainly members of the vitamin B-complex and vitamin C) may play a role in modifying key cellular events occurring during wound healing. The results seem to suggest that these vitamins may accelerate the healing process, and lead to positive structural changes in the composition of the collagenous network of healing wounds. Nonetheless, several issues related to the regulation and sequencing of such potential effects are still not clear. Additional studies addressing the specific interactions between the cellular elements and healing events are needed to elucidate such potential effects.

Effects of nutrition on periodontal disease onset, progression and response to treatment

Data from research have provided possible mechanisms in which nutrition may influence periodontal disease onset, progression, and wound healing. For example, it has been suggested that in response to periodontal pathogens, the polymorphonuclear leukocytes (PMN) elaborate destructive oxidants, proteinases, and other factors. The balance between these factors, the antioxidants, and endogenously synthesized antiproteinases determine the extent of periodontal damage (Page 1991, Lamster & Novak 1992). Malnutrition is characterized by marked tissue depletion of the key antioxidant nutrients, including gamma-glutamyl-cysteinyl-glycine (GSH), and impaired acute-phase protein response to infections (Bruun et al. 1999). Acute-phase protein response plays a key role in promoting healing, and its deficit in malnutrition is due to impairment in the production and cellular action of the cytokines (Albina 1994). Other features of malnutrition include inverted helper-suppressor T-cell ratio, histaminemia, hormonal imbalance with increased blood and saliva

levels of free cortisol, and defective mucosal integrity (Bagley 1996, Dowsett 1996, Boynton et al. 1999). Malnutrition has the potential to influence the prognosis of periodontal infections adversely (Enwonwu 1994). Additionally, malnutrition elicits adverse alterations in the oral microbial ecology as well as in the volume and the antibacterial and physicochemical properties of saliva (Enwonwu 1995).

Studies in the periodontal literature have attempted to assess the relationship between various nutritional elements and periodontal status and/or response to therapy. A review of these studies with critical appraisal of their methodology and results follows.

Vitamin B-complex

Studies evaluating the possible role of vitamin B-complex supplementation on periodontal health are summarized in Table 3. Vogel (1976) evaluated the effects of vitamin B_c supplementation in humans. On days 0 and 30 of a double-blind study, two groups of 15 subjects each were evaluated using plaque index (PI), gingival index (GI), gingival crevicular fluid (GCF) flow, and fasting plasma folic acid levels. One group received 2 mg of vitamin B_c twice daily for 30 days, while the control group received a placebo. The results of this study indicated that vitamin B_c supplemented to the diet might increase the resistance of the gingiva to local irritants, since less gingival inflammation was seen in the experimental group. However, the subjects from this study were left untreated and the possible effects of vitamin B_c supplementation on healing and response to therapy could therefore not be observed (Vogel 1976).

Dreizen et al. (1977) observed the effects of vitamin B_3 deficiency on the periodontium. Adult cotton top marmosets were made vitamin B_3 deficient by long-term dietary deprivation. The results showed that the animals developed a syndrome characterized by anorexia, weight loss, weakness, diarrhea, dermatitis, enterocolitis, and stomatitis. The stomatitis was highlighted by a necrotizing gingivitis and periodontitis and by an ulcerative and atrophic glossitis. These results showed a possible predisposition of the periodontium to aggressive forms of periodontal disease due to a deficiency of vitamin B_3 intake (Dreizen et al. 1977). Since this was an animal study, therefore, the presence of the same effects in human remains to be determined.

The effects of a vitamin B_3-supplemented toothpaste treatment on the gingival blood circulation of plaque-induced gingivitis were evaluated in a nonhuman primate model (Taguchi 1989). A 1% nicotinate ethyl ester paste (nicotinate paste), a 0.5% chlorhexidine paste as an antibacterial agent, a mixture of the two pastes, and the base alone as a control were used. The results showed that the nicotinate paste, chlorhexidine paste, and the mixed paste seemed to reduce gingival inflammation as assessed by the blood flow, hemoglobin amount, and GCF amount compared with the control paste. These results showed a positive influence of local administration of vitamin B_3 in the presence of gingival inflammation. Vitamin B_3-supplemented toothpaste showed similar results to the positive control group that used a 0.5% chlorhexidine paste (Taguchi 1989).

The effect of a 28-day period of systemic and topical vitamin B_c supplementation on gingival inflammation during pregnancy was also investigated (Pack 1980, Thomson 1981, 1982). Thirty pregnant females in their 32nd week of pregnancy were randomly divided into three groups. One group received placebo mouthwash and placebo tablets; another group received placebo mouthwash and one 5 mg vitamin B_c tablet daily; and a third group received placebo tablets and rinsed with vitamin B_c mouthwash twice daily for 1 min. The vitamin B_c mouthwash group showed highly significant improvement in GI despite no significant changes in PI. Dietary vitamin B_c was similar in all groups. Since no significant changes were observed in PI, and the vitamin B_c-supplemented groups showed a significant reduction in GI, it was concluded that vitamin B_c can improve the resistance of the periodontium to bacterial plaque (Pack 1980, Thomson 1981, 1982).

Pack (1984) later developed a double-blind study to determine the effects of a vitamin B_c mouthwash (5 mg/5 ml, twice daily for 4 weeks) on established gingivitis in nonpregnant adults. Dietary analysis showed that few subjects ingested greater than 200 μg of vitamin B_c daily. The results showed that the

Table 3. Effects of vitamin B-complex on periodontal disease

Author	Sample	Comparision	Results
Dreizen et al. (1977)	monkeys	vit. B_3 (−)	vit. B_3 (−) animals developed ANUG and ANUP
Taguchi (1989)	monkeys	vit. B_3 toothpaste in induced gingivitis study	greater GI reduction in experimental group
Vogel (1976)	humans	vit. B_c (+) versus placebo	lower GI in experimental group
Thomson (1981)	humans	vit. B_c (+) versus placebo	greater GI reduction with no changes in PII in experimental group
Pack (1984)	humans	vit. B_c mouthwash versus placebo in patients with established gingivitis	greater GI reduction in experimental group
Pack (1986)	humans	vit. B_c mouthwash versus placebo in patients with experimental gingivitis	no significant differences between test and placebo groups
Drew (1987)	humans	systemic versus topical vit. B_c versus placebo in patients with gingival overgrowth	inhibition of gingival overgrowth: topical > systemic > placebo
Backman (1989)	humans	systemic vit. B_c versus placebo in patients with gingival overgrowth	gingival overgrowth significantly reduced in experimental group
Brown et al. (1991a, b)	humans	systemic vit. B_c versus placebo in patients with gingival overgrowth	no significant differences between test and placebo groups
Popell et al. (1991)	humans	systemic vit. B_c versus placebo in patients with gingival overgrowth	greater reduction of gingival overgrowth in experimental group

(+) = supplementation; (−) = deficiency.

vitamin B_c mouthwash appeared to have an influence on gingival health through local rather than systemic influence (Pack 1984). A later study (Pack 1986) showed that a 0.1% vitamin B_c mouthwash did not have any statistically significant effects on accumulated plaque or clinical signs of experimental gingivitis. The author attributed the different response of experimental gingivitis to vitamin B_c mouthwash, compared with the response of established gingivitis already reported, to the experimental gingivitis study design that may not represent an authentic replica of the cellular and immunological responses occurring in established gingivitis (Pack 1986).

Drew (1987) conducted a double-blind study to quantify clinically the effects of both systemic and topical administration of vitamin B_c on phenytoin-induced gingival overgrowth in man. For a period of 6 months, one group of patients received two daily topical applications of a vitamin B_c solution. An additional group received two daily doses of systemic vitamin B_c, while a control group received placebo medication. The results indicated that throughout the 180-day period of the study, topical vitamin B_c significantly inhibited gingival overgrowth to a greater extent than either the systemic vitamin B_c or placebo groups (Drew 1987). A similar finding was also reported by Backman (1989), who suggested that folate levels should be checked and supplementation with vitamin B_c considered in patients on long-term anticonvulsive diphenylhydantoin therapy (Backman 1989). On the contrary, Brown et al. (1991a, b) found a single daily oral 3 mg capsule of vitamin B_c did not show efficacy as the sole therapeutic agent in the reduction of phenytoin-induced gingival overgrowth (Brown, et al. 1991a, b). Poppell et al. (1991) examined the effect of vitamin B_c supplementation on the recurrence of phenytoin-induced gingival overgrowth following gingivectomy. Although the treatment group had significantly less recurrence of gingival overgrowth ($p \leqslant 0.05$), the mean differences amounted to only 6–7% at 3 and 6 months (Poppell et al. 1991). Since plaque control of mentally disabled subjects can be considered less than ideal, the possible effects of vitamin B_C supplementation on periodontal healing in patients with adequate plaque control could not be observed.

These studies have shown some of the potential influences of vitamin B-complex on periodontal disease onset, progression, and treatment. However, more controlled studies are needed to support the strength of association of such influences.

Vitamin C

Data from animal studies and from studies of patients with acute necrotizing ulcerative gingivitis (ANUG) have provided suggestive evidence for an association between ascorbate deficiency and disease risk. Melnick et al. (1988) developed a case–control study of plasma ascorbate and ANUG on 60 patients with a history of ANUG infection and 60 age–race–sex-matched controls. The results showed that patients with a history of ANUG ingested less vitamin C, as compared with healthy controls. Further, there is biological plausibility for such an association, due to the role of ascorbate in collagen synthesis and leukocyte function. Consequently, several studies have attempted to study the degree of association between vitamin C and periodontal status and response to therapy (Table 4).

The effects of vitamin C deficiency in periodontal tissues were first studied by Glickman (1948a). Guinea pigs were placed on a vitamin C-free diet and sacrificed after 35 days. Histological examination revealed the formation of deeper periodontal pockets in animals deficient in vitamin C. Gingival edema and hemorrhage were also seen in the test group. In addition, when gingivitis was induced in vitamin C-deficient pigs, the test group showed

Table 4. Effects of vitamin C on periodontal disease

Author	Sample	Comparision	Results
Dreizen et al. (1977)	monkeys	vit. B_3 (−)	vit. B_3 (−) animals developed ANUG and ANUP
Glickman (1948a)	guinea pigs	vit. C (−) diet versus normal diet	deeper PD in experimental group
Glickman (1948b)	guinea pigs	vit. C (−) in induced gingivitis study	increased CAL in experimental group
Waerhaug (1958)	monkeys	vit. C (−) in induced gingivitis study	increased bone loss and gingivitis in experimental group
Vogel (1979)	humans	4-day diet survey of periodontitis versus healthy patients	daily AA intake of periodontitis patients was similar to healthy subjects
Ismail & Eklund (1983)	humans	NHANES periodontitis versus health	weak association between AA intake and periodontitis
Woolfe et al. (1984)	humans	nondeficient subjects vit. C mega doses	no significant differences between test and placebo groups
Vogel et al. (1986)	humans	nondeficient subjects Vit. C mega doses	no significant differences in PMN chemotaxis
Leggott et al. (1986)	humans	vit. C (−)	GI directly related to AA status
Melnick et al. (1988)	humans	subjects with history of ANUG	history of ANUG positively associated with lower AA intake
Leggott et al. (1991)	humans	vit. C (−) 4-day diet	BOP increased after AA (−), returning to normal after AA repletion
Nishida et al. (2000a)	humans	NHANES III periodontitis versus health	weak, but statistically significant, relationship between AA intake and periodontal disease in smokers
Sheiham et al. (2001)	humans	epidemiological data dentate versus edentate	AA consumption significantly lower in the edentate group, and plasma ascorbate levels significantly correlated with edentulism

AA: ascorbic acid; PD: probing depth; CAL: clinical attachment level; BOP: bleeding on probing.

increased periodontal destruction when compared to controls (Glickman 1948b). The author attributed this exaggerated periodontal destruction to an inability to form a peripheral connective tissue barrier, a reduction in inflammatory cells, a diminished vascular response, and the inhibition of fibroblast formation and differentiation to form osteoblasts. Waerhaug (1958) also observed that when gingivitis was induced in vitamin C-deficient monkeys, an increased osteoclastic resorption rate and hemorrhage occurred. These results showed that a deficiency of vitamin C can predispose to the occurrence and exacerbation of periodontal disease (Waerhaug 1958).

Leggott et al. (1986) investigated whether systemic levels of vitamin C influence periodontal health in humans. Eleven healthy, nonsmoking men, aged 19 – 28 years, eating a rotating 7-day diet adequate in all nutrients except vitamin C were observed. No mucosal pathoses or changes in plaque accumulation or probing depths were noted during any of the periods of depletion or supplementation. However, measures of gingival inflammation were directly related to the ascorbic acid status. The results suggested that ascorbic acid may influence early stages of gingivitis, particularly crevicular bleeding (Leggott et al. 1986). Leggott et al. (1991) also described the relationship between varying vitamin C intakes, periodontal status, and subgingival microflora. No significant changes in plaque accumulation, probing pocket depth, or attachment level were noted when different vitamin C groups were compared. In contrast, gingival bleeding increased significantly after the period of vitamin C depletion and returned to baseline values after the period of vitamin C repletion. However, no relationship could be demonstrated between either the presence or proportion of target periodontal microorganisms and measures of bleeding or vitamin C levels (Leggott et al. 1991).

It has been reported that the use of megadoses of vitamin C in normal human subjects does not have a predictable or strong effect on the gingival response to initial therapy (Woolfe et al. 1984). Similarly, megadoses of ascorbic acid supplementation did not influence PMN chemotaxis or responses to experimental gingivitis (Vogel et al. 1986). In order to determine a possible link between vitamin C intake and periodontal status, Vogel & Wechsler (1979) compared 4-day nutrition surveys of 35 periodontitis patients and 1222 general population subjects. The means for both groups were found to be above the recommended daily allowances (RDA). The calcium-phosphate ratio for the periodontal group was 0.62 (ideal = 1), and 13 of the 35 subjects had deficient calcium intake. The daily dietary intake of periodontitis patients was not significantly different from the general population (Vogel 1979). Ismail et al. (1983) also found only a weak association between periodontal disease and vitamin C deficiency in the analysis of nutritional and periodontal health data collected from a representative sample of the US population. Intake of ascorbic acid in amounts larger than those recommended by the dietary standards did not seem to be associated with better periodontal health (Ismail et al. 1983).

More recently, Nishida et al. (2000a) evaluated the role of dietary vitamin C as a contributing risk factor for periodontal disease utilizing the Third National Health and Nutrition Examination Survey (NHANES III). A sample of 12,419 adults (20 – 90 years of age), with dental measurements and assessment of dietary information as well as demographic and medical histories, were included in the studies. Using multiple logistic regression analysis, a relationship between reduced dietary vitamin C intake and increased risk for periodontal disease for the overall population (odds ratio = 1.19) was found. Current and former tobacco users who were taking less dietary vitamin C showed an increased risk of periodontal disease with an OR of 1.28 for former smokers and an OR of 1.21 for current tobacco users. There was a dose–response relationship between the levels of dietary vitamin C and periodontal disease with an OR of 1.30 for those taking 0 – 29 mg of vitamin C per day, to 1.16 for those taking 100 – 179 mg of vitamin C per day as compared to those taking 180 mg or more of vitamin C per day. The authors concluded that dietary intake of vitamin C showed a weak, but statistically significant, relationship to periodontal disease in current and former smokers as measured by clinical attachment levels (Nishida et al. 2000b).

Sheiman et al. (2001) assessed the National Diet and Nutrition Survey to determine if there is a relationship between dental status in people 65 years and older and intake of certain nutrients. Intake of protein, calcium, and vitamin C was significantly lower in edentate subjects, and people with 21 or more teeth consumed more of most nutrients. This relationship in intake was not apparent in the hematological analysis. However, plasma ascorbate was significantly associated with dental status (Sheiham et al. 2001).

Since the antibacterial and physicochemical properties of saliva are compromised in chronic malnutrition, Enwonwu et al. (1994) examined the possibility that some malnutrition-induced changes in salivary gland function are potentially capable of promoting growth and metabolic activities of pathogenic oral microorganisms. Compared to well-fed controls, rats fed a 3% protein diet for 18 days showed a significant reduction in the submandibular gland arginase (L-arginine amidinohydrolase, EC 3.5.3.1) activity, associated with a marked increase (+85%) in the glandular level of free arginine. Since many oral bacterial species, some of which are dominant plaque microorganisms, utilize the arginine deiminase (EC 3.5.3.6) pathway, increased availability of free arginine from salivary glands offers a plausible explanation for the frequently reported observation of differential overgrowth of several potentially pathogenic microorganisms, including some mutant streptococci in protein-deficient laboratory animals, and may well apply to similar findings in malnourished populations (Enwonwu 1994, Enwonwu et al. 1994).

Enwonwu et al. (1995) observed male guinea pigs subjected to prolonged marginal ascorbic acid deficiency. Compared with age- and sex-matched controls fed an adequate diet for a similar period, ascorbate deficiency had no effect on submandibular gland weight, but elicited a significant reduction in stimulated whole-saliva flow rate. Plasma cortisol concentration (nmol/l) was significantly increased in the deficient animals. This suggested that increased salivary and blood levels of glucocorticoids may reduce the ability of the host to mount an effective immune response to oral pathogens (Enwonwu 1995).

Studies evaluating the role of vitamin C on periodontal status appear to indicate that a weak, yet statistically significant, effect may be present. However, studies evaluating the effects of vitamin C supplementation on the

Table 5. Effects of dietary calcium on periodontal disease

Author	Sample	Comparision	Results
Dreizen et al. (1977)	monkeys	vit. B_3 (−)	vit. B_3 (−) animals developed ANUG and ANUP
Abe et al. (1989)	rats	dietary calcium (−)	increased osteoclastic activity in experimental group
Amano et al. (1989)	rats	dietary calcium (−)	increased osteoclastic activity and unchanged bone apposition rate in experimental group
Vogel (1979)	humans	4-day diet survey	13 out of 35 subjects showed less than ideal calcium intake
Uhrbom & Jacobson (1984)	humans	dietary calcium (+) in untreated subjects	dietary calcium (+) failed to reverse the effects of periodontitis
Nishida et al. (2000a, b)	humans	NHANES III dietary calcium intake and periodontitis	weak, but statistically significant, relationship to periodontitis (OR: 1.84–1.99)
Krall et al. (2001)	humans	dietary calcium and vit. D (+)	decreased tooth loss in experimental group

OR: odds ratio.

response to periodontal therapy have largely failed to show a strong association between such supplements and clinically relevant improvements in therapeutic results. Prospective, controlled clinical trials with well-defined comparison criteria may be needed to further evaluate the presence, and strength, of such an association.

Dietary calcium

Animal as well as human studies of calcium intake, bone mineral density, and tooth loss provide a rationale for hypothesizing that low dietary intake of calcium is a risk factor for periodontal disease (Henrikson 1968, 1969, Baer 1977, Ostreicher 1981, Aleo et al. 1984). Studies evaluating this hypothesis are listed in Table 5.

Oliver (1969) described the effects of deficiencies of calcium, vitamin D, or calcium and vitamin D and of variations in the source of dietary protein on the periodontium of rats. When the diet was deficient of calcium and vitamin D, alveolar bone changes resembling osteoporosis and a reduction in the number and diameter of the periodontal ligament fibers were observed. The deficiency in vitamin D alone had no obvious effect on periodontal tissues. These observations implied a possible influence of dietary calcium-deficient diets and susceptibility to periodontal disease progression (Oliver 1969).

Abe et al. (1989) observed the alveolar bone changes in rats subjected to a dietary calcium-deficient diet, and reported that with only 7 days of calcium deficiency, higher osteoclastic activity was found among calcium-deficient rats when compared to controls (Abe et al. 1989). Amano et al. (1989) reported similar findings using the same study model.

Osborn et al. (1977) were the first to evaluate dietary calcium intake among periodontal patients. Analyzing the nutrients in 5-day diet diaries of 100 patients from a private periodontal practice, they found that calcium intake below the RDA was common among periodontal patients (Osborn et al. 1977). Uhrbom & Jacobson (1984) investigated whether dietary calcium supplementation was able to reverse the effects of periodontal disease in untreated patients. One-third of the subjects showed low calcium intake, and even among these patients, dietary calcium supplementation failed to reverse the effects of chronic periodontal disease (Uhrbom & Jacobson, 1984).

More recently, Nishida et al. (2000a, b) evaluated the role of dietary calcium intake as a contributing risk factor for periodontal disease utilizing the NHANES III data. The relationship between low dietary calcium intake and increased levels of periodontal disease showed an estimated odds ratio of 1.84 for young males, 1.99 for young females, and 1.90 for the older group of males. A dose response was seen in females, where there was 54% greater risk of periodontal disease for the lowest level of dietary calcium intake and 27% greater risk in females who took moderate levels of dietary calcium as compared to those who took 800 mg or more dietary calcium per day (Nishida et al. 2000a). Krall et al. (2001) recently reported the results of a large longitudinal placebo-controlled clinical trial. Subjects received dietary calcium and vitamin D supplementation, and after 5 years the experimental group showed significantly less tooth loss when compared to controls.

The results of these studies seem to suggest that low dietary intake of calcium may result in more severe progression of periodontal disease. However, the effects of dietary calcium supplementation on the arrest of signs of periodontal disease or as adjunctive aids in its treatment have not been thoroughly evaluated. Further controlled studies may be warranted to assess such effects.

Conclusion

Although relatively little attention has been given by periodontal research, the medical literature has studied the effects of nutritional supplementation among patients receiving various treatment modalities, and at present nutrition is considered to play an important role in wound healing processes. The effects of nutrition on periodontal disease status and response to treatment have been studied using different methods and study models. Several studies have reported various degrees of association between nutritional elements/supplements and periodontal status, and others have reported possible positive influences of nutritional supplementation on periodontal therapeutic outcomes. However, data from these studies should be interpreted with caution. Most of the results are mainly based on cross-sectional, case–control, and animal studies. Recent cross-sectional reports by Nishida et al. (2000 a, b) were able to demonstrate a weak but significant relationship between ascorbic acid and dietary calcium intakes and increased susceptibility for the development of periodontal disease. Randomized, controlled, longitudinal trials are needed to categorize malnutrition as a "risk

factor'' for periodontal disease. Furthermore, since periodontal disease is dependent on host susceptibility, prophylactic nutrient supplementation for the prevention of periodontal disease onset and progression is still not indicated. Prospective clinical trials comparing treated patients with an optimal nutrition to patients without the same care are needed to provide scientific evidence for nutritional supplementation among periodontal patients. In addition, studies should also examine how specific nutritional supplements may influence treatment (e.g. nonsurgical and surgical periodontal therapies, guided tissue regeneration, dental implants) outcomes. Considering that nutrient supplementation shows minimal or no side effects, if future prospective, controlled clinical trials are able to demonstrate that it could be used to enhance response to therapy, such supplementation may prove valuable in producing more predictable treatment outcomes. In conclusion, although periodontal disease is not a nutritional deficiency disease per se, malnutrition is likely to play a role in either predisposing the host to the progression of preexisting periodontal lesions, influence the outcome of periodontal treatment, or both.

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Zusammenfassung

Einfluss Spezieller Ernährung auf Beginn, Verlauf und Behandlung Parodontaler Erkrankungen

Es konnte gezeigt werden, dass der Beginn, der Verlauf und das Ansprechen auf therapeutische Intervention parodontaler Erkrankungen durch verschiedene modifizierende systemische, lokale und Umweltfaktoren beeinflusst werden. Ergänzungen zur Ernährung wurden als mögliche Einflussfaktoren für den parodontalen Status und die Wundheilung diskutiert. Diese Arbeit gibt eine Übersicht über die verfügbare Literatur zum Einfluss spezieller Elemente der Ernährung (z.B. Vitamin-B-Komplex, Vitamin C und Kalzium) auf die generelle Wundheilung, parodontale Erkrankungen sowie das Ansprechen auf parodontale Therapie. Verschiedene Studien haben über Zusammenhänge zwischen Elementen der Nahrung bzw. Ernährungsergänzungen und dem parodontalen Status berichtet. Andere berichten über mögliche positive Einflüsse von Ernährungsergänzungen auf das Ergebnis parodontaler Therapie. Besonderer Wert wird auf die kritische Bewertung der vorhandenen Studien gelegt und es werden Empfehlungen für zukünftigen Forschungsbedarf gegeben, um die Existenz und Ausprägung von Zusammenhängen zwischen Ernährung und parodontaler Gesundheit vollständig zu erfassen. Daten, die aus der Literatur gesammelt wurden, legen den Schluss nahe, dass eine Ergänzung der Ernährung minimale oder keine Nebenwirkungen hat. Allerdings die Wirksamkeit einer prophylaktischen Ernährungsergänzung für die Prävention der Entstehung und Progression von Parodontitis oder die Verbesserung der parodontalen Wundheilung muss noch bestimmt werden.

Résumé

Effets de substances nutritives spécifiques sur l'apparition de la maladie parodontale, sa progression et son traitement

L'apparition, la progression et la réponse de la maladie parodontale aux interventions thérapeutiques sont influencées par différents facteurs systémiques locaux et environnementaux. L'apport supplémentaire de substances nutritives a été suggéré comme facteur influençant l'état parodontal et la guérison. Cette étude revoit la littérature concernant les effets des éléments nutritionnels spécifiques comme le complexe vitaminique-B, le vitamine-C et le calcium diététique sur la guérison en général, l'état de la maladie parodontale et la réponse au traitement parodontal. Différentes études ont rapporté différents degrés d'association entre les éléments/suppléments nutritifs et l'état parodontal, et d'autres ont rapporté des influences positives possibles des suppléments nutritionnels sur la guérison thérapeutique parodontale. L'importance est axée sur l'appréciation critique d'études disponibles et sur une recommandation en recherches futures pour explorer davantage la présence et la force de l'association entre la nutrition et la santé parodontale. Des données collectées de la littérature suggèrent que l'apport de suppléments nutritifs n'est suivi que de peu ou pas d'effets secondaires. Cependant, l'efficacité d'un supplément nutritif prophylactique pour la prévention primaire et de la progression de la maladie parodontale, ou pour l'augmentation de la guérison parodontale reste à déterminer.

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