A Critique of 25 Years of Research Which Culminated in the Successful Therapy of Periodontal Disease with Coenzyme Q₁₀

Karl Folkers**

Abstract: Periodontal disease involves inflammation of tissues which support the teeth, and in primarily caused by the accumulating bacterial plaque on the teeth. The extraction of teeth is the end stage. Current statistics show that about 60% of young adults and 80% of adults in the U. S. have periodontal disease, i.e., this disease is not limited just to the older generations.

The initially available Coenzyme Q₇ (CoQ₇) was clinically found to improve therapeutically severe and destructive periodontal disease. CoQ₇ had been found to show 80-100% of the activity of Coenzyme Q₁₀ (CoQ₁₀) for NADH-oxidase.

The partially synthetic hexahydro-CoQ₄ (H₆CoQ₄) became abundantly available for clinical research, although it showed only 10-25% of the activity of CoQ₁₀ for NADH-oxidase. Over ca. five years, H₆CoQ₄ was clinically tested, including a double-blind trial, for therapy of periodontal disease, and was found to cause such extraordinary healing that H₆CoQ₄ was considered as conjunctive therapy for ordinary dental practice.

It had been determined that there was a statistically significant deficiency of CoQ₁₀-enzyme activity in gingival biopsies from patients with periodontal disease in comparison to control. In due time, CoQ₁₀ became available for clinical studies on therapy of periodontal disease. After an open trial of treating periodontal disease with CoQ₁₀, which was interpreted to the effect that healing was—"dramatically accelerated"—and was—"very impressive", a successful double-blind trial was conducted with capsules of CoQ₁₀ and a matching placebo.

Subsequent trials were concluded with the observation that—"CoQ₁₀ could well become an essential modality of prevention and treatment of periodontal disease".

These open and double-blind trials were largely based upon criteria of periodontal score, tooth mobility, gingival index and pocket depth. Recently, the bleeding index was another criterion of therapy, and the result was positive.

Currently, the reduction of subgingival microorganisms has been recorded, and concomitantly, it was recorded that CoQ₁₀ increased the levels of the T₄/T₈ ratio and that of IgG.

The repeatedly demonstrated successful therapy with CoQ₁₀ of periodontal disease is evident from several criteria showing reduced disease, from criteria of an improved immune system, and restored periods of natural prevention of disease.

CoQ₁₀ is, therefore, recommended for both prophylactic and therapeutic treatment of periodontal disease.

Introduction

Periodontal disease involves inflammation of the tissues which support the teeth. The periodontium is the supporting structure of the teeth including the gingiva, alveolar bone, and periodontal ligament. This disease frequently begins as gingivitis and progresses to periodontitis. Other diseases, for example, diabetes mellitus, somehow can enhance periodontal disease.

* 本論文は、大阪大学歯学部常光雄教授が平成4年3月末をもって停年退官されるにあたり、その業績を讃えるために寄稿したものである。
** Institute for Biomedical Research, The University of Texas at Austin, Texas.
Periodontal disease is caused by bacterial plaque (emphasis on bacteria) which accumulates and adheres to the teeth. The disease results in local immunopathologic destruction of connective tissues and the bacterial antigens penetrate the periodontal tissues and initiate an inflammatory state. Gingival bleeding occurs. Ultimately, there is destruction of alveolar bone, the periodontal ligament, or a loss of support for the teeth. The extraction of teeth is the end stage. Periodontal disease is no longer considered to be a disease of just the aging population, but rather the destruction caused by bacterial plaque regardless of age.

Prophylaxis consists of good oral hygiene, and treatment has been with anti-microbial mouth washes, for example with chlorohexidine. Other clinical diseases and certain commonly used drugs may intensify periodontal disease with CoQ10 is based upon restoration of the immune system, and is superior to anti-microbial therapy, a critique of this new therapy with CoQ10, based on intrinsic biochemistry and the immune system, is timely.

Early Research with Coenzyme Q10

Lenaz et al.1) found that CoQ10 is at the "break-point" in activity of members of the CoQ group for activity in DPNH-oxidase. However, CoQ10 was available in the late '60s to support animal and clinical research when the "human CoQ10" was not available in needed amounts. In 1967, Tanner2) reported that rats treated with citric acid developed periodontal lesions. In 1968, Tsunemitsu et al.3) described the protection afforded by CoQ10 not only to rats having experimental periodontitis, but to some patients having natural periodontal disease. Akiyoshi et al.4) in 1968, described the effect of CoQ10 on pathologic changes of the periodontal tissues of guinea pigs which were maintained on a diet deficient in vitamin C. Tsunemitsu and Matsumura5) found that the hypercitricemia and clinical status in 25 patients with severe and destructive periodontal disease was improved when treated with CoQ10. Nakamura et al.6) reported the data on a phosphatase and a transaminase of periodontal tissues in guinea pigs having scurvy. In 1976, Wilkinson et al.7) summarized the results of a double-blind administration of CoQ10 and a placebo which were adjunctively administered with normal periodontal therapy to patients with periodontitis. All patients receiving CoQ10 or placebo were correctly assigned before decoding. The improvements in pocket depth (combined pocket analysis) and the number of pockets (greater than 4 mm) were significant; 0.01<p<0.05. This was the first double-blind test of CoQ10 in the U. S. A. It was concluded that CoQ10, like CoQ10, appears useful in conjunction with standard periodontal therapy for patients. Two periodontists, on general dentist and two paraprofessionals participated in the assignments. The clinical assignments before decoding were not difficult.

Early Research on Hexahydrocoenzyme Q4

Before CoQ10 was clinically available, H6CoQ4 was administered to one patient with edematous tissue and gingival bleeding. Since H6CoQ4 is considerably less active than CoQ10 (10-25 % for DPNH-oxidase), 1000 mg of H6CoQ4, formulated in corn oil, was administered for one month, and then this dosage was reduced to 500 mg, which was continued. There was "improvement" from this treatment; Littarru et al., 19718).

In 1973, Matsumura et al.9) of the Department of Preventive Dentistry of the Osaka University Dental School and Nakamura and Folkers of the Institute for Biomedical Research, University of Texas at Austin, conducted a double-blind study on 13 patients who received H6CoQ10 and 11 patients who received a placebo. Nine of the 13 patients treated with H6CoQ10 were significantly improved, five by p<0.001, one by p<0.01, two by p<0.02, and one by p<0.05. In comparison, only three of the 11 patients on placebo improved by p<0.05. The therapeutic improvement of the patients with periodontal disease on treatment
with H\textsubscript{2}CoQ\textsubscript{4} was better both in the number of improved patients and the degree of improvement than for those patients on placebo. Furthermore, all of the symptoms for 4/13 of the H\textsubscript{2}CoQ\textsubscript{4}-treated patients had completely disappeared after the therapy of 8 weeks. When all eight symptoms of the H\textsubscript{2}CoQ\textsubscript{4}-treated group were analyzed, all symptoms had improved, \(p<0.01\). It was emphasized that oral hygiene alone can benefit the bacterial component of periodontal disease, but not a gingival deficiency of CoQ\textsubscript{10}.

In 1975, Iwamoto et al.\textsuperscript{10} described the positive clinical results of the administration of H\textsubscript{2}CoQ\textsubscript{4} to a 25-year old Caucasian with uniquely severe and chronic periodontal disease, which required extraction of all teeth. During the fourth and fifth examinations after the seventh and eighth week of periods of treatment, three dentists separately and independently scored the clinical improvements of five symptoms by significance of \(p<0.01\) to \(p<0.001\). The initial clinical benefit of treatment with H\textsubscript{2}CoQ\textsubscript{4} was observed at the time of the second examination after three weeks of therapy. Iwamoto et al. concluded that treatment with H\textsubscript{2}CoQ\textsubscript{4} could be an important therapeutic adjunct to periodontal therapy.

In 1975, Wilkinson and Arnold of the Department of Periodontics of the David Grant USAF Medical Center, Travis AFB, CA. and Folkers et al.\textsuperscript{11} described excellent results from treating seven periodontal patients with CoQ\textsubscript{10} and one with H\textsubscript{2}CoQ\textsubscript{4} by the oral route. The periodontal score decreased (\(p<0.01\)) and unexpectedly, the periodontal pocket depth decreased (\(p<0.05\)). All eight patients had been considered candidates for surgical intervention. The healing was so excellent, 5-7 days post-biopsy, that the biopsy sites were difficult to locate. It was concluded that the healing was extraordinarily effective. The mean value of the specific activities of the succinate dehydrogenase-CoQ\textsubscript{10}-reductase of the gingival biopsies had increased (\(p<0.05\)) during the therapy, and which appeared to correlate with the extraordinary healing. Wilkinson and Arnold concluded that treatment of periodontitis with CoQ\textsubscript{10} should be considered as adjunctive therapy in ordinary dental practice.

**Early Research with Coenzyme Q\textsubscript{10}**

In due time, CoQ\textsubscript{10} became available in larger quantities to clinical support studies on periodontal disease. In 1971, Littarru et al.\textsuperscript{8} reported that gingival biopsies from 13 patients, 18-62 years, and having from minor to severe periodontal disease, revealed a deficiency of CoQ\textsubscript{10} in contrast to biopsies of normal periodontal tissue which showed no deficiency. Nakamura et al., in 1973\textsuperscript{12}, in cooperation with Dr. Wilkinson, a practicing dentist, determined the activities of the succinate dehydrogenase-CoQ\textsubscript{10} reductase. The corresponding data from 15 individuals as controls, who did not have periodontal disease in comparison to levels of controls (0.001<\(p<0.01\)). These data justified continuing clinical studies on the administration of CoQ\textsubscript{10} to patients with periodontal disease.

Nakamura et al.\textsuperscript{12} reported that about 60 % of diseased gingival tissues from 40 patients with periodontal disease showed a deficiency of CoQ\textsubscript{10} at its site in the succinate-CoQ\textsubscript{10} enzyme. Of 24 control biopsies from individuals who did not have periodontal disease, 20 % showed deficiencies of CoQ\textsubscript{10}. However, as a group, the tissues from the control individuals showed a negligible deficiency of CoQ\textsubscript{10}.

The deficiency of CoQ\textsubscript{10} at the succinate site of the diseased gingival tissue was considered to probably be just the result of a classical nutritional deficiency in the body.

Wilkinson et al.\textsuperscript{13} gave a presentation on the use of CoQ\textsubscript{10} for the therapy of periodontal disease. The dentists responsible for treating periodontal disease with CoQ\textsubscript{10} were particularly impressed with the observation that healing was "dramatically accelerated" and was "very impressive".

**Continued Clinical Research on Coenzyme Q\textsubscript{10}**

In 1976, Wilkinson et al.\textsuperscript{14} conducted a double-blind trial with CoQ\textsubscript{10} and a matching placebo on a group of 18 patients with periodontal disease. The trial was significantly positive (\(p<0.01\)). Before decoding, all eight patients receiving CoQ\textsubscript{10} and 7/10 patients receiving placebo were correctly assigned. The remaining three patients on placebo showed mild improvement which could have been due to better hygiene. Crevicular fluid flow as a measure of response was newly monitored. Pocket-depth, periodontal
health, calculus, and the plaque score provided the data for evaluation.

In 1976, Hansen et al.\(^{15}\) determined the specific activities of the succinate dehydrogenase-CoQ\(_{10}\) reductase in mitochondria which were derived from diseased gingival biopsies of patients with periodontal disease. The criteria for selection were patients having a bone score of 1.0-4.0, and a pocket depth of 2.5-5.2 mm. All 29 patients showed a deficiency of 20-63 % of CoQ\(_{10}\)-enzyme activity in the gingival biopsies. The mean value was elevated (p<0.001) over that of control. The corresponding blood samples, 24/28 (86 %) showed deficiencies of 20-66 %, and a higher mean value (p<0.001) than that of controls. It was concluded that periodontal patients frequently have significant gingival and leukocyte deficiencies of CoQ\(_{10}\). Such deficiency is perhaps more likely caused by a systemic nutritional imbalance rather than neglected oral hygiene, although poor oral hygiene may be a contributing aspect. Such gingival deficiency could predispose this tissue to periodontitis and support previous conclusions on the adjunctive use of CoQ\(_{10}\) with oral hygiene.

In 1977, Folkers et al.\(^{16}\) emphasized the need for an effective treatment of periodontal disease. Even in 1977, it was generally believed that bacterial plaque is the primary or only direct cause of periodontal disease, and that the attempted control of the plaque by oral physiotherapy can be unsuccessful for some patients in periodontal practice. A survey on all the knowledge up to that time supported the conclusion of Wilkinson et al. in 1976 that therapy of deficiencies of CoQ\(_{10}\) by oral CoQ\(_{10}\) can be adjunctive therapy for extraordinary healing. The indispensability of the intrinsic CoQ\(_{10}\) in bioenergetics was emphasized as the basis for the extraordinary healing, and the dental benefit resulting from the administration of CoQ\(_{10}\) to periodontal patients.

In 1977, Folkers et al.\(^{17}\) surveyed the progress in the United States and in Japan on the research on the clinical use of CoQ to treat periodontal disease.

Since statistics\(^{17}\) showed that about 60 % of young adults and 80 % of middle aged people in the United States have periodontal disease, presumably the same incidence occurs in Japan. Oral-physiotherapy can be ineffective. A significant deficiency (p<0.001) of CoQ\(_{10}\) in diseased gingival tissues has been repeatedly found. Over the years, the clinical administration of three forms of CoQ (CoQ\(_{10}\), CoQ\(_{7}\), H\(_2\)CoQ\(_{4}\)) has been conducted by practicing dentists and periodontists with the common conclusion that CoQ is therapeutically beneficial. Six double-blind trials involving these three forms of CoQ were conducted with significant results. The trial with the "human CoQ\(_{10}\)" was particularly significant (p<0.01).

The study of the periodontal patients which showed that 100 % had a gingival deficiency and 80 % also had a leukocytic deficiency of CoQ\(_{10}\) was intellectually orienting. A gingival deficiency of CoQ\(_{10}\) appears to predispose this tissue to periodontitis, particularly during neglected oral hygiene. It was concluded that CoQ\(_{10}\) can improve bioenergetics and can prophylactically and adjunctively be used for extraordinary healing during routine periodontal therapy.

In 1981, Wilkinson et al.\(^{18}\) evaluated all the chemical and physical measurements that had been and can continue to be used in evaluation of the effectiveness, or lack of it, of CoQ\(_{10}\) and possibly other biochemicals, to treat periodontal disease.

In 1981, Iwamoto et al.\(^{19}\) reported on a double-blind study in Japan with 56 patients at the Hiroshima University Dental Hospital. The daily dosage of CoQ\(_{10}\) was 60 mg. The score of tooth mobility was significantly lower in the group treated with CoQ\(_{10}\) than in the group treated with placebo. The differences were significant at four weeks (p<0.05) and at 12 weeks (p<0.05). The difference in pocket depth was also significant at four weeks (p<0.05). It was considered that the administration of CoQ\(_{10}\) might cause an increase in the level of citric acid which, in turn, might favorably influence healing. It had previously been known that citric acid exerted a healing effect on the periodontal pockets in dogs subjected to an experimental trial.

In 1983, Shizukuishi et al.\(^{20}\) enlarged the information on experimental periodontitis in dogs. This group induced experimental periodontitis in dogs by the use of cotton floss. In a control group, the cotton floss ligatures were left around the teeth during a 28-day period. CoQ\(_{10}\) was administered daily for two
weeks to the dogs that had the periodontitis which resulted from the ligatures. The results indicated that the oral administration of CoQ10 to the dogs was effective in suppressing advanced periodontal inflammation as assessed by the gingival index and the pocket depth. The activity of the CoQ10-dependent enzymes was significantly elevated in the control group, and the CoQ10-percent deficiency of the succinic cytochrome-c reductase in the CoQ10-treated group was restored to a normal level.

Nylander and Nordlund, in Sweden\(^2\), treated six patients with a daily oral supplement of 30-100 mg of CoQ10 who had varying degrees of periodontal disease. They found that this dosage of ubiquinone attenuated the degree of the tendency for bleeding and/or inflammation of the gingiva. The time needed for supplementation with ubiquinone for therapeutic effect varied for these six individuals. This pilot study showed that CoQ10 does have a role in the treatment of periodontal disease. It was emphasized that ubiquinone should not replace the use of odontological care, and that dentists should view ubiquinone as a compliment both for therapeutic and prophylactic treatment of varying degrees of periodontal disease.

Apparently, Nylander has been the first investigator in this field to use the bleeding index as a criterion of the therapeutic benefit of CoQ10 for periodontal disease.

In 1992, McRee et al.\(^2\) determined, in the first such research, whether the administration of CoQ10 to patients with periodontal disease would reduce the levels of subgingival microorganisms. They conducted two clinical trials on the oral administration of 100 mg of CoQ10 daily to 22 patients with periodontal disease for two months, and to 11 such patients for six months. In the two-month trial, the gingival index decreased \((p<0.001)\) and the pocket depth also decreased \((p<0.001)\), but the plaque index did not change. Subgingival microorganisms, identified as motile rods, decreased \((p<0.01)\) and the spirochetes also decreased \((p<0.02)\).

In the second trial with 11 patients for six months, the gingival index was decreased \((p<0.01)\) after both two- and six-month periods, and the pocket depth was decreased after two months \((p<0.05)\) and six months \((p<0.01)\), but the plaque index was unchanged after both the two- and six-month periods. Motile rods decreased after two months \((p<0.01)\) and six months \((p<0.05)\). The number of patients \((N=11)\) in the six-month trial was necessarily, but unfortunately, limited.

It was concluded that this CoQ10-therapy to reduce periodontal disease, and particularly the microorganisms, is preferable to ordinary treatment with anti-bacterial agents, because CoQ10 therapy improves the immune mechanisms to control disease.

In a companion manuscript to the one by McRee et al.\(^2\) Hanioka et al.\(^3\) summarized the biochemical evidence which supported the effective therapy by McRee et al. with CoQ10 which revealed reduction of the subgingival microorganisms of patients having periodontal disease. The rationale for the two trials, for two months and for six months, respectively, was the existing knowledge that CoQ10 is intrinsic and indispensable to the human immune system, and that patients with periodontal disease have impaired immune systems. In the first trial with 22 patients for two months, the T4/T8 ratio was increased \((p<0.001)\), and the CoQ10 blood level increased \((p<0.001)\).

In the second trial with 11 patients, which was appraised after both two and six months, the T4/T8 ratio was increased after two months \((p<0.01)\) and after six months \((p<0.05)\), and the IgG level was increased only after six months \((p<0.05)\). The CoQ10 levels were increased \((p<0.001)\) after both the two- and six-month periods.

This effective therapy with CoQ10 of periodontal disease was evident from reduced disease, an improved immune system, and restored periods of natural prevention of disease.

**Acknowledgement**

Appreciation is expressed to the Robert A. Welch Foundation of Houston, Texas for their support of this research.
References


