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Letter to the Editor

Cardiovascular diseases, oxidative stress and antioxidants: the decisive role of coenzyme Q_{10}

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In his timely article [1], Dr. P.K. Singal reviews the relationship between oxidative stress, antioxidants and cardiac diseases. This field is the most extensively investigated area of cardiovascular research with consequential practical therapeutic ramifications. Unfortunately, the author's presentation of the clinical effectiveness of various antioxidants in the prevention or restriction of the molecular, cellular and systems effects of oxidative stress is limited. An essential omission is the absence of any reference to the involvement and the well-studied clinical applications of coenzyme Q_{10} in various forms of cardiovascular diseases — a subject of great interest for the readers of this publication.

Coenzyme Q_{10} (CoQ_{10}, ubiquinone) is a naturally occuring, fat-soluble nutrient (a quinone), with characteristics that are common to vitamins and, like vitamins, is essential to the optimal functioning of an organism. CoQ_{10} is a potent and versatile antioxidant that is present in humans and in some animals. In addition to its antioxidant function, CoQ_{10} plays an indispensable role in intracellular energy production. Being a vital electron and proton carrier, CoQ_{10} supports adenosine triphosphate synthesis in the mitochondrial inner membrane and stabilizes cell membranes, thus preserving cellular integrity and function. Most CoQ_{10} clinical research is focused on the large, heterogeneous group of cardiovascular diseases. The first report of such a clinical trial was published 30 years ago. Since 1960, 14 international symposia have been organized and the proceedings have been published. This represents a collection of more than 4100 pages of technical contributions on various medical and clinical aspects of CoQ_{10}. As a result, the relationship between cardiac CoQ_{10} deficiency, cardiovascular diseases and their amelioration by CoQ_{10} treatment was demonstrated.

More recently, the results of 34 controlled clinical trials and many open-label and long-term studies were reviewed [2]. The largest study to date involves 2359 patients and the participation of cardiologists in 173 Italian hospital centers. A table summarizing the current indications for clinical use of CoQ_{10} in various forms of cardiovascular diseases is presented in Ref. [3]. The table also includes drug-induced (anthracyclines and others) cardiomyopathies, subject of considerable assessment by Dr. Singal. The exclusion of CoQ_{10} again is an indefensible issue.

Despite the well-known high risk of cardiomyopathies and, ultimately, congestive heart failure incidence associated with doxorubicin (DR, adriamycin) treatment, this cytotoxic anthracycline antibiotic is still widely included in most cancer clinical regimens because of its efficacy and broad-spectrum activity.

Results from the mid-1970s, reviewed by Olson et al. [4], indicate strongly that DR produces free radicals in microsomal systems and it was postulated that, because of recycling, one DR molecule forms many free radical molecules. They are capable of causing lipid peroxidation, especially at the mitochondrial level, resulting in morphological as well as functional mitochondrial injury. The end result of this injury is the clinically critical disintegration of the intramitochondrial bioenergetic process. The heart, with its high energy demand, is more susceptible to injuries caused by free radicals. Olson et al. [4] also noted that free radical scavengers attenuate DR-induced cardiac dysfunction, thus contributing to the acceptance of today's well-confirmed theory for the causal involvement of free radicals in many pathological processes, ranging from neoplasia to aging, and their amelioration following the administration of antioxidants.

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As early as 1974, two reports [5,6] indicated that DR also restricts mitochondrial respiration by nearly 100% as a result of inhibition of CoQ-enzymes in the mitochondria of heart tissue. Consequently, two other publications [7,8] demonstrated that, in vitro and in vivo, CoQ_{10} supplementation prevented the inhibition of CoQ-enzymes resulting from DR treatment. Furthermore, it was shown [9] that rats receiving DR and CoQ_{10} did not develop electrographic changes, indicating a protective effect.

In 1978, Cortes et al. [10] reported that treatment of patients with DR and CoQ_{10} resulted in a decreased incidence of cardiac dysfunction. This study was followed by many clinical trials, confirming and amplifying this CoQ_{10} effect. A study by Karlsson et al. [11] established that patients treated with DR have lower tissue CoQ_{10} contents in heart, skeletal muscle and in blood than healthy controls. The authors concluded that the lower the heart muscle CoQ_{10} level, the more impaired was the cardiac function, thus again demonstrating a relationship between DR-induced cardiac injury, CoQ_{10} functional deficiency and clinical compensation with CoQ_{10} supplementation.

Other studies indicated that CoQ_{10} treatment does not abrogate the antitumor effect of DR. In contrast, it is expected that this effect will be enhanced, since it was reported (reviewed in [12,13]), that CoQ_{10} is a potent modulator of the immune system's effectiveness in neoplasia, infections (including retroviral) and in aging. Since then, this concept has been confirmed in experimental and clinical studies, including those in cancer patients [14,15]. More specifically, treatment of experimental animals with CoQ_{10} reverses the inhibition of the antibody response caused by DR administration, thus indicating a compensation of the profound immunosuppression, another ground for concern during DR treatment of cancer patients [13].

We should note here that, in the old clinical trials, a lower CoQ_{10} dose was used (30–100 mg/day). Today, because of excellent tolerance of patients and product availability, much higher doses are recommended (200–600 mg/day and even higher).

Lastly, Dr. Singal in his article discusses the therapeutic efficacy of vitamin E and other antioxidant vitamins in various forms of cardiovascular diseases. An interesting earlier observation, not cited in this article, is that CoQ_{10} induces the regeneration of the utilized vitamin E from α-tocopheroxyl radicals, thus amplifying the vitamin E antioxidant effect, a process that otherwise must rely on access of water-soluble antioxidants, such as ascorbate. Furthermore, evidence has accumulated that CoQ_{10} prevents both the initiation and the propagation of lipid peroxidation, whereas vitamin E acts exclusively as a chain-breaking antioxidant, inhibiting propagation. The intriguing CoQ_{10}-vitamin E link was reviewed by Ernster et al. [16].

In our opinion, based on the review of the extensive literature and our personal experience for more than 20 years, treatment of patients with various forms of cardiovascular diseases by a combination of CoQ_{10} and other antioxidants, concomitant with standard drug treatment, is justified and recommended.

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